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THE POWER AND THE PROMISE

AHFMR MISSION STATEMENT

We support a community of researchers who generate knowledge that improves the health and quality of life of Albertans and people throughout the world.

Our long-term commitment is to fund basic, patient and health research based on international standards of excellence and carried out by new and established investigators and researchers in training.

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ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

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June 1993

. . . OF MEDICAL RESEARCH IN ALBERTA

This publication is a report card and a textbook.

Officially, it is the third Triennial Report of the Alberta Heritage Foundation for Medical Research, accompanied by the second Report of the International Board of Review.

This is also designed as a resource for junior and senior high school science students. To that end, the achievements of AHFMR researchers are reported as they fit into the exciting new developments in human biology. As well, some of the researchers share what life in the lab is really like, so young Albertans can consider research careers.

Some day soon, we will be helping to train some of them, just as AHFMR has already supported thousands of summer and full-time student researchers in Alberta universities.

THE POWER

. . . **of Creativity**: 155 talented scientists from Canada and around the world who competed with the best to become AHFMR researchers.

. . . **of Molecular Biology**: Learning to control the switches that start cancer, let in a virus, boost the immune system, cause the body to turn against itself in diabetes or arthritis – and more.

. . . **of Technology**: Watching nerve cells grow, wire-tapping signals of the heart muscles, computer-designing drugs, building vaccines with protein "Lego-sets", watching killer cells attack tumors – and much more.

. . . **of Success**: AHFMR researchers reaping the rewards of excellence with international honors and millions of outside research dollars from public and industry sources – now two dollars for every AHFMR dollar invested.

. . . **of a Vision**: That Alberta could become a world centre of medical research. It has happened.

THE PROMISE

. . . **Patient Care**: AHFMR researchers will continue to raise the quality of health care in Alberta, caring for patients and making new knowledge available to health care professionals.

. . . **Prevention**: As part of the international science community, AHFMR researchers will develop new vaccines, discover new drugs with greater potency and fewer side effects, and find new ways to detect who is susceptible to disease for preventive treatment before it appears or early treatment before it is severe.

. . . **Economic Benefits**: More and more Albertans will make a living from medical research-related science and technology, expanding the commercialization of innovations.

. . . **Decision-Making**: As Alberta medical researchers open new options for treatment and evaluate old ones, there will be more knowledge to inform policy decisions about health care.

. . . **Status**: AHFMR researchers will continue to bring prestige and financial resources to Alberta.

FROM THE Chairman

On behalf of the Trustees of the Alberta Heritage Foundation for Medical Research, I am pleased to present the Triennial Report, covering our activities from 1990 to 1993.

We are proud of the accomplishments of AHFMR researchers, who are making Alberta a world leader in medical research and patient care; who are significantly contributing to a science-, technology-, and knowledge-based economy in Alberta; who are creating new opportunities for young Albertans in research careers.

This report demonstrates we are indeed accomplishing our goals and fulfilling the promise of medical research, while remaining accountable to the people of Alberta through the provincial government, which provided us with our endowment in 1980.

To address accountability, and wisely use our resources, this report has been written for use as a textbook in Alberta senior and junior high schools, as part of our science education activities for young people.

This Triennial Report will be followed by the report of the second International Board of Review (IBR), published in September 1993. The IBR evaluation is conducted every six years to ensure that AHFMR activities meet international standards of excellence and fulfill our mandate – to generate knowledge that improves the health and quality of life of Albertans and people throughout the world.

Alvin G. Libin
CHAIRMAN

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FROM THE *President*

Mr. Alvin Libin (*left*) and Dr. Matthew W. Spence

This Triennial Report shows AHFMR-supported scientists are on the leading edge of medical research in the genetics of cancer, infectious diseases, nerve regeneration and several other areas. It shows that the promise of molecular biology and other basic studies, combined with patient and population health research, is opening up exciting new approaches to healing.

AHFMR and the researchers we support work in partnership with many research, health, government and community organizations, and with scientists and community leaders on the provincial, national and international scene. Most particularly we rely on partners in the Universities of Alberta and Calgary, and on our own dedicated Board of Trustees.

Our accomplished scientists belong to the interconnected community of international science. With the combined efforts of many, beginning with the Government of Alberta which had the foresight to establish such a unique institution, AHFMR has put Alberta on the world map for medical research. All of us are reaping the benefits of the knowledge generated.

Dr. Matthew W. Spence, M.D., Ph.D.
PRESIDENT

KEEPERS OF THE PROMISE:

BLAZING A TRAIL

IN THE EARLY FALL OF 1963, YOUNG LORNE TYRRELL planned to register for medical school, but Dad called him home to help on the farm in central Alberta. Dad had bought a bulldozer and the contract with an Indian band to build a road didn't come through until the first week of classes. Dr. Tyrrell recalls:

> "The chief had surveyed the road by breaking tree branches over the middle of where he wanted it to go. I had never built a road and here I was at 8:00 in the morning sitting on a cat, not knowing where to start. In my nervousness, I ate all my lunch!
>
> "Then I started pushing the road and it was a real challenge. When one of the tracks came off, I had to jack up the cat for a whole day, and somehow get the track onto the sprockets. I learned to solve problems that seem insurmountable. After a week, it really began to look like a nice road."

Promising Hepatitis Drug

WORLD FIRST

Some twenty years later, Dr. Tyrrell is blazing a trail for the world in virology research and he has not forgotten his early lessons on the cat. Dr. Tyrrell and colleagues have developed the world's first anti-hepatitis B drug, currently being tested in patients with chronic liver disease. Preliminary results are promising.

Presently there are no effective drugs for hepatitis B, carried by 300 million people in the world, 100,000 of them Canadians. Chronic carriers have no symptoms and carrying the virus creates a risk for cirrhosis and liver cancer.

A Dream Come True

"This is the culmination of a dream," Dr. Tyrrell told the audience at the opening of the Glaxo Heritage Institute for Virology at the University of Alberta in October 1992.

On the strength of his pioneering work on hepatitis B, and the excellent Alberta research community, largely in place of because of $500 million of AHFMR support over the last 12 years, Glaxo Canada made the Institute possible with an initial $800,00 for construction, $550,000 a year for operating expenses, and a promise of up to $15 million if studies proceed as well as anticipated.

Dr. Tyrrell, who is also Chairman of the Department of Medical Microbiology and Infectious Diseases, heads the Institute which will eventually number about 30 people. Initially, Dr. Tyrrell was joined by two AHFMR researchers, molecular biologist Dr. John Elliott and AIDS researcher Dr. Lung-Ji Chang.

Continued on page 8

Dr. John Elliott (*left*), and Dr. Lorne Tyrrell

Mama's Ducks and Other Helpers

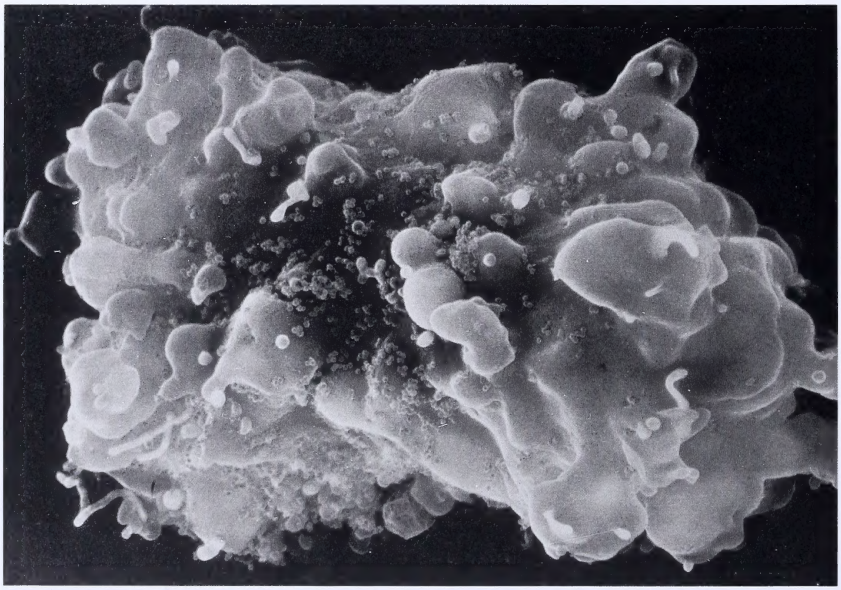
Dr. Tyrrell emphasizes that successful medical research is a team effort over time. The story of his world first – discovering a drug for hepatitis B – shows how medical research works.

He was inspired by compassion for his patients – he had no effective drug to help them – and by his enthusiastic medical students. While teaching, he realized the textbooks didn't have the whole scoop on hepatitis B: there could be a new way to screen compounds for it.

Inspiration and help came from other places. Mama – Mrs. Tyrrell – originally kept son Lorne's ducks (the research model for testing compounds against hepatitis B) on the family farm. Chemist Dr. Morris Robins, formerly of the U of A and now at Brigham Young University, produced the compounds and still collaborates. Insights by students, Dr. Satoru Suzuki and Dr. Weixing Luo were crucial. Then, at the right time, AHFMR provided a technology commercialization grant which helped attract industry. Glaxo asked him to screen compounds licensed from Biochem Pharm of Montreal.

In the same way, the Institute team will be backed by the expertise of U of A chemists, biochemists, microbiologists and immunologists. With the funds and the people, Dr. Tyrrell does not see many viruses as insurmountable. More roads will be blazed.

"When you have this kind of opportunity your farfetched ideas become realistic. Now we say, 'We can do that!' We're just tossing ideas around about how we might be able to neutralize the AIDS virus....The principles we developed to deal with AIDS could be applied to other viruses difficult to treat – CMV, Epstein Barr virus (causes mononucleosis) and hepatitis C."



The AIDS virus (*tiny dots*) destroys a helper T cell.

TOP AIDS RESEARCHER JOINS INSTITUTE

Dr. Lung-Ji Chang is determined to defeat the talented, wiley HIV virus and he's going to do it in Alberta. He has left the largest medical research centre in the world, the National Institutes of Health, in Maryland, to join Dr. Tyrrell and Dr. Elliott in the Glaxo Heritage Institute.

The HIV virus is so deadly because it attacks the immune system, the very part of the body designed to fight viruses. HIV destroys helper T cells called CD4 cells, by entering the cells, then hijacking their genetic machinery to produce more viruses. So far, HIV has defeated experimental vaccines mainly because it mutates so easily.

Dr. Chang has evidence that CD4 cells are not the only way HIV enters cells. He is using genetically engineered HIV and "carrier" genes to investigate other ways the virus attaches to cells and penetrates them. This information could lead to new drugs or vaccines.

He has a long term hope, based on the fact that the virus can remain latent so long. "My thinking is: we're not going to find a way to eliminate the virus from the infected person. But I think we can find some kind of chemical that will suppress the virus and prolong the latency. The average latency is now 10 years; if we could prolong that to 30 years, AIDS would not be such a severe problem."

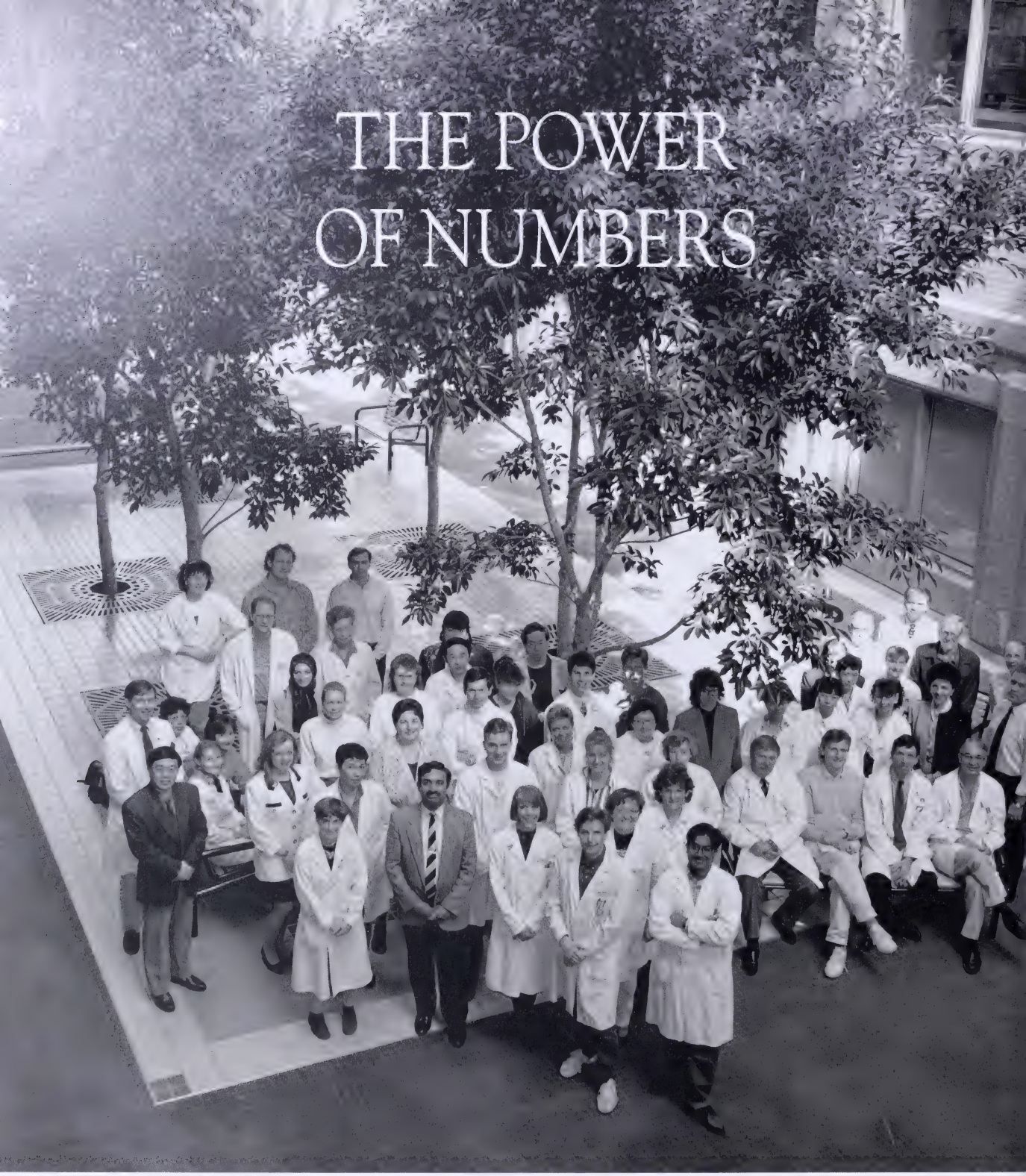
Dr. Lung-Ji Chang

MOLECULAR BIOLOGY TO THE RESCUE

Dr. John Elliott is passionate about applying his outstanding expertise in cloning genes and characterizing proteins to clinical problems. Most of the time, he is developing an efficient vaccine for another scourge of the world, malaria. In the Glaxo Heritage Institute, his molecular biology talents are helping Dr. Chang pull out the genes that regulate how HIV penetrates host cells.

Dr. Elliott's skills and creative approaches to problems in the research group illustrate the synergy that produces results. He says, "We can bounce ideas off one another and pool our expertise and creativity. For me, that's the most exciting part about participating in the Institute."

THE POWER OF NUMBERS



The Arthritis and Joint Injury Research Group, University of Calgary

WHAT IF YOU HAD A DISEASE THAT WAS AS ANCIENT AS PREHISTORIC TIMES and more common than cancer, but despite all the wonders of modern medical care doctors weren't sure what to do about it?

You would want masses of medical researchers to take a new look, to stand on their heads if necessary, to see this old disease in a new light. That's what's happening at the McCaig Centre at the University of Calgary.

The disease is arthritis, sometimes mild, sometimes severe, and occasionally fatal. It appears in 100 forms, the most common being osteoarthritis and rheumatoid arthritis.

One in six Canadians has arthritis or a joint injury that could lead to the disease later in life, costing $7 billion annually in medical care and lost productivity. A new case appears every 30 seconds.

Despite its prevalence, we know far less about arthritis than we do about cancer or heart disease. Researchers in the Arthritis and Joint Injury group are changing that.

Looking Every Which Way

The U of C group is unique in North America because it uses a double power: the power of numbers and the power of seeing problems from different points of view. More than 60 researchers come from different disciplines: basic science, orthopedic surgery, rheumatology, engineering and rehabilitation medicine.

Together they are covering the whole spectrum of joint injury and disease, from understanding the basic molecular events which give rise to disease to the best kind of care – self-care – and the best medical cure – prevention.

Research focuses on three goals: to improve diagnoses of arthritis so earlier treatment is possible; to improve treatments and prevent problems through more effective healing of injuries and other means; and to understand the mechanics of joint repair.

Community Support

When the Calgary community realized what the U of C team could do, private and corporate donors gave the McCaig Centre $2.8 million. With support from the University and $7.5 million from AHFMR over 10 years, the power of numerous funding partners has given the arthritis and joint injury research team the backing it needs to advance knowledge and improve care.

The Most Advanced Patient Care

WORLD FIRST

The team offers Southern Albertans the most advanced care. Consider Susan de Waal, Calgary mother of four daughters. She was given another functional wrist after her own was removed because of a bone tumor. Chris Schollaardt is the first Western Canadian to have transplanted ligaments in a knee smashed in a construction accident. Joanne Reimer bore a healthy child after three consecutive miscarriages, because Dr. Marvin Fritzler found they were caused by lupus autoantibodies in her blood, though she does not have the disease. (Lupus is a type of arthritis.) With treatment for the antibodies during Mrs. Reimers' fourth pregnancy, Christopher Reimer was born.

These were all "world-firsts" in patient care.

Continued on page 13

"There's no cure for arthritis, but if you feel in control you will feel better," says Yvonne Caffrey.

A sufferer of rheumatoid arthritis, Mrs. Caffrey is a role model for others with the disease as she leads groups in a course on "Self-Management of Arthritis", as part of a Calgary program initiated by Dr. Steve Edworthy and the Arthritis Society. The course covers exercise, nutrition, communicating with doctors, pain management techniques, and most of all, the importance of attitude.

When we have an unsolvable medical problem, we want more medical research and we want to find out where the best care is available. With the McCaig Centre, Albertans with arthritis and joint injury problems won't need to look to the Mayo Clinic or the Scripps Clinic or anywhere else. The best care will be here.

"We are making a difference. We think our approach is the right approach," says Dr. Marvin Fritzler, one of the AHFMR researchers who helped found the Centre.

"We don't understand why this multidisciplinary approach is not happening in other centres," says Dr. Cy Frank, founding Director of the group, now led by Dr. David Hart.

AHFMR DISCOVERIES

Advanced Diagnostics

WORLD FIRST

Labs from around the world send Dr. Marvin Fritzler serum samples to analyze for lupus autoantibodies, using a sophisticated system he pioneered. Prior to this molecular analysis, lupus was often misdiagnosed, sometimes for years, because it affects many parts of the body and mimics other diseases.

Dr. Fritzler has also identified rheumatoid arthritis autoantibodies and some of the molecules they interact with. These may be useful for identifying the developing disease even before symptoms are present, providing new opportunities for preventive treatment.

Dr. Frank has found that the "noises" knees make may be used to identify developing arthritis or other joint problems in knees.

Magnetic Resonance Imaging is being studied to see if the technology can detect joint injuries and osteoarthritis. If so, could replace or supplement expensive invasive surgery.

Ligament Healing

Dr. Frank has developed new methods to quantify the healing process in ligaments and determined what variables will enhance healing of transplanted ligaments. Dr. Robert Bray has shown that blood flow to ligaments affects healing.

The team has shown that disuse of ligaments can alter growth and healing, a concern for injured children put in casts for long periods of time.

Patient Care

Dr. Marvin Fritzler and Dr. Steve Edworthy founded the Lupus Clinic at the U of C where patients are given specialized care. Drs. Frank and Bray offer arthroscopic knee surgery to patients, and both men care for athletes in the U of C Sports Medicine Centre.

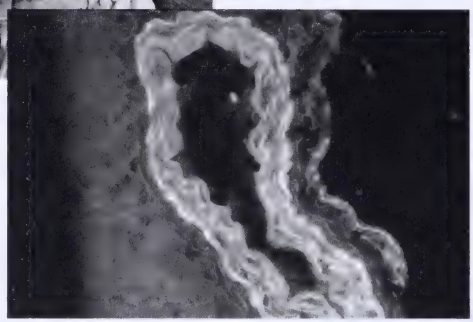
Dr. Edworthy, a rheumatologist AHFMR supported during research training at Stanford University, is advancing quality patient care on other fronts as well.

He and colleagues have examined how hip replacements affect function and quality of life. They have developed new guidelines for deciding who should receive the surgery, an important consideration for containing costs while maintaining patient well-being.

Dr. Ron Zernicke has developed a way to help patients recover a more normal gait to prevent further stress on the good hip.

Mrs. Joanne Reimer (shown here with son Christopher), had three unexplained miscarriages after bearing a healthy daughter. Dr. Marvin Fritzler discovered Mrs. Reimer carries lupus autoantibodies in her blood, though she has no clinical signs of the disease. When she became pregnant again, Dr. Fritzler prescribed a drug used for lupus.

The pregnancy was successful and Christopher Reimer was born. "It was like a miracle," recall Mrs. Reimer and her husband, Tim.



Lupus autoantibodies

Prevention and quality of life are addressed in a self-help community program for people with arthritis, modelled on a Stanford program. Dr. Edworthy and others have found that some arthritis patients are handicapped by their attitude, a learned helplessness that affects their emotional and physical well-being. If people are taught how to manage their disease, they feel more in control and become more active, which keeps them healthier longer.

Dr. Edworthy, Dr. Frank and Dr. Bray were all AHFMR-supported in their early years for specialty research training abroad. They have acquired the best expertise available, brought it back to Alberta and added to it.

Now researchers from elsewhere come to study with them.

Chronic Pain

For people with arthritis, managing pain is a daily challenge. In an AHFMR public lecture to Calgarians, international pain expert Dr. John Loeser explained that too many doctors and patients don't realize chronic pain and acute pain are different. Treating chronic pain as acute pain may lead to additional disability. Rest and inactivity make chronic pain worse. Opiates, muscle relaxants and other drugs useful in acute tissue injury may even add to depression and cognitive deficiencies.

Director of the Multidisciplinary Pain Centre at the University of Washington Medical Centre, Dr. Loeser gave the lecture as part of AHFMR's public education services.

POWER OF THE PUMP:

THE HEART OF THE MATTER

WHAT DO WE KNOW OF THE HEART?

We can be warm-hearted, cold-hearted, hard-hearted, light-hearted, heavy-hearted, stout-hearted, faint-hearted, tender-hearted or broken-hearted. Over history, hearts have been eaten for courage, buried for honor and, according to the Egyptian Book of the Dead, weighed for merit.

The heart has always entered the domain of metaphor and mysticism because it is the life centre, recognized even by Cro-Magnon man, who painted a heart of the bison on cave walls.

The heart is a technical masterpiece, probably the most perfect machine known to humankind. This durable, life-giving pump beats at least 100,000 times a day, about 3 billion times in a lifetime to send blood surging through 95,000 kilometres of blood vessels. That's about twice the earth's circumference.

Each of us has 95,000 kilometres of blood vessels.

In modern biology, the heart is intimately known right down to the tiny currents (one billionth of an amp) that generate heart beats. We have learned to keep people alive with cardiac drugs, surgery, pacemakers, transplanted hearts, and even temporary artificial hearts. Yet there is still a mystery at the centre of the event called sudden cardiac death, the single most frequent killer.

AHFMR scientists are at the forefront in understanding the dangerous heart beats, called arrhythmias, which lead to a heart attack. This is the science of electrocardiology because heart muscles pump when the heart generates tiny electrical currents. These currents are created when sodium, potassium and calcium ions move across each of the 10 million cardiac cells.

AHFMR cardiac teams have devised new ways to measure this activity in single cells in the lab and in patients. This gives them the means to test how existing drugs and pacemakers alter the life-threatening rhythms and to devise more effective treatments. It has allowed them to test the latest generation of implantable pacemakers.

The dual expertise of basic researchers and physicians who treat patients and bring their problems back into the lab to be solved has made the Universities of Alberta and Calgary centres for international clinical trials of cardiac drugs.

With the techniques of modern biology, the goal is not just to treat heart attack patients, but to prevent the attacks from occurring.

The other arm of prevention, controlling disease through a healthy lifestyle, is becoming a happy fact for many Canadians. With education, they are learning to reduce risk of heart disease by eating properly, exercising adequately, not smoking, and managing stress. Research shows that people are changing their behavior, and heart disease is being significantly reduced.

Getting back to what we know of broken hearts, American researchers have reported that heart attack survivors who had mates were far less likely to die from a second attack than people who lived alone.

AHFMR DISCOVERIES

Guardian Angel of the Heart

Corinne Swinarton is alive because she carries a battery-operated rescue device that monitors and regulates her heart rhythms. If she has a heart attack, this device, called a pacemaker/defibrillator, delivers a life-giving shock to resume the heart's electrical activity.

AHFMR teams at the Foothills and U of A Hospitals have been testing these devices and making the most up-to-date models available to Albertans like Mrs. Swinarton.

Dr. Katherine Kavanagh has shown that the electrical therapy delivered by pacemaker/defibrillators will work with less power than existing models. This means the devices can be made smaller and the shock will no longer feel like "being kicked by a horse," as one patient put it.

Mrs. Corinne Swinarton

Will this cardiac drug save my life?

Maybe yes, maybe no. It depends on many things. Maybe we can find something better.

Doctors have a battery of drugs for cardiac diseases, ranging from the centuries old drug, digitalis, to the newer antiarrhythmic drugs. The drugs work for some, but not everyone, and they have side effects. Deciding what drug to prescribe has, in the past, been largely a matter of trial and error but AHFMR researchers are changing that.

- Using technology he has developed, Dr. Wayne Giles is one of the few people in the world who can observe how a drug affects the electrical activity in a single cardiac cell, only five millionths of a millimetre across.
- Dr. Anne Gillis has shown that dietary intake of fats alters the effects of antiarrhythmia drugs given to people at risk for heart attacks.
- Dr. Roland Auer has evidence that insulin given immediately after a stroke could reduce brain damage.
- Dr. Gary Lopaschuk has shown that drugs to increase the heart's carbohydrate use during and after bypass surgery, or following a heart attack, could reduce damage caused by lack of blood flow to the heart.

Echoes of the Heart

Survivors of a heart attack are often at risk because the damaged heart bulges and thins, making it difficult to pump. Dr. Bodh Jugdutt and other scientists have shown that nitroglycerin and other drugs reduce the dangerous bulging by unloading the heart in the early stages of healing.

Dr. Jugdutt can watch how the drugs improve healing in a video of the pumping heart, made with ultrasound imaging called 2-D echocardiography.

World Looks to Alberta for Cardiac Drugs on Trial

Basic lab work shows how old and new drugs actually affect the electrical activity of the heart.

After the lab work, the answer lies in numbers, testing drugs with hundreds of thousands of patients in double-blind clinical trials in an international effort. Because of their expertise, AHFMR teams at the U of A and the U of C are invited to participate in Canadian and international trials, and in some cases they lead them. Trials are addressing such questions as: Who does digitalis help, and how? Can drugs given to people with left ventricular function, but no signs of heart failure, prevent them from developing the problem?

The U of A Lipid and Lipoprotein Group: (*left to right*) Dr. Dennis Vance, Dr. Robert Ryan, Dr. Gary Lopaschuk, Dr. David Brindley, and Dr. Shinji Yokoyama (*seated*). (Dr. Zemin Yao is missing.)

The Cholesterol Question

We used to worry about clean teeth, clean feet and a clean conscience. Now we have to worry about clean arteries. So we've learned to eat properly and exercise adequately. Will we be rewarded with clear arteries?

The chances are much higher, but there's no guarantee because the cholesterol story is extraordinarily complicated. Consider this: Winston Churchill could eat, drink and smoke until he was 90, but some very fit athletes have heart attacks in their thirties. The reason is probably in their genes.

Cholesterol is a waxy, oily substance produced by the liver and acquired through food, particularly red meat, egg yolk, and whole milk products. It is a key component of cell membranes but if it excessively accumulates in blood vessel cells – a process that begins in the teenage years or sooner – there is great risk of a heart attack or stroke.

Cholesterol is a fat (researchers call it a lipid) and because it's insoluble in water, it is carried through the body in a complex of molecules called lipoproteins. Excess low-density lipoproteins (LDL) place one at high risk for atherosclerosis, but high-density lipoproteins (HDL) seem to protect against the disease. Your genes partly determine your ratio of LDL to HDL, and researchers have identified several of the key genes.

After it's produced in the liver, cholesterol goes through a series of conversions and is delivered to body tissues, then transported back to the liver. There are many points in these pathways to intervene and alter it. That's why AHFMR researchers and others are trying to sort out the basic process.

WORLD FIRST

Dr. Dennis Vance is the first in the world to discover several liver enzymes that regulate the manufacture of cholesterol. Dr. Shinji Yokoyama is learning how the body naturally removes cholesterol from cells to form HDL, so that the process can be enhanced. Others are devising new techniques to study the key apolipoproteins that carry cholesterol.

These studies could not be pursued without the new tools of genetics and molecular biology. Researchers are convinced that, once we understand this complicated cholesterol business, we can outsmart it.

Unblocking Arteries More Safely

Dr. Alexandra Lucas is searching for better ways to clear arteries and to identify developing plaque earlier for more effective treatment. Current treatments such as by-pass surgery and balloon angioplasty are not ideal because they involve some risk. Moreover, the plaque often grows back.

A cardiologist, Dr. Lucas has evidence that a technology called laser-induced fluorescence can show doctors precisely where the plaque is, for safer surgery and for monitoring the progress of disease or healing. Dr. Lucas has also tested two new cutting tools for clearing arteries invented by Edmonton engineers.

The Stress Effect

According to Dr. David Brindley, increasing dietary cholesterol and fats magnifies the sensitivity of animals to stress stimuli. This is related to the stress-induced increase in fats in the blood and associated atherosclerosis. Two compounds decrease body weight and stress responses, lower fats in the blood and improve insulin sensitivity. This may make the animals less at risk for blocked arteries.

Who should take cholesterol-lowering drugs?

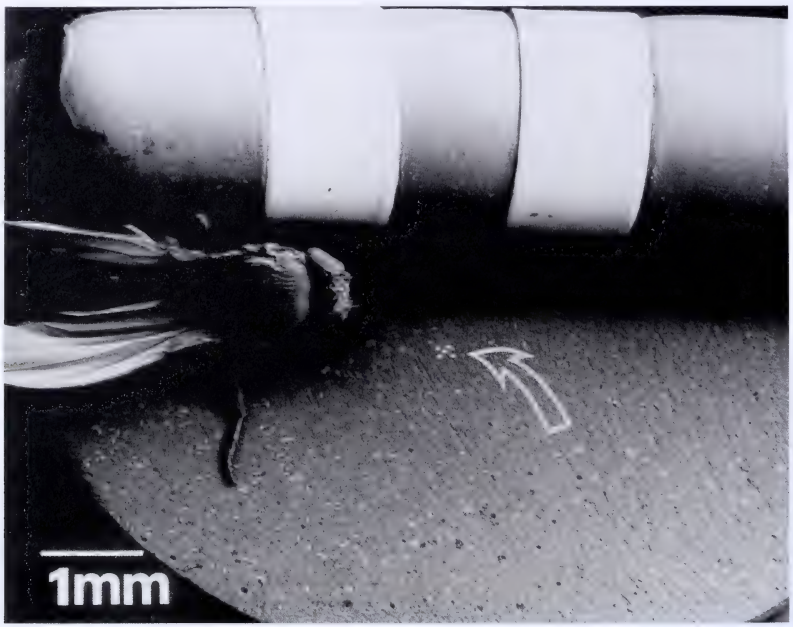
About two-thirds of people who have coronary artery or heart disease have normal or almost normal cholesterol levels. Would giving them cholesterol-lowering drugs be a benefit? Possibly, but the benefits must override the risks and the high costs of treating the hundreds of thousands of people who fit the category.

To find the answer, Dr. Shinji Yokoyama and Dr. Koon Teo have mounted a clinical trial at the University of Alberta.

Smaller Than a Fruit Fly's Eye

The arrow in this diagram points to five tiny electrodes invented by Dr. Frank Witkowski to record, for the first time ever, electrical currents across cell membranes in intact heart tissue. This tool allows him to study the heart rhythms which cause sudden cardiac death and see how they are modified by drugs or pacemakers.

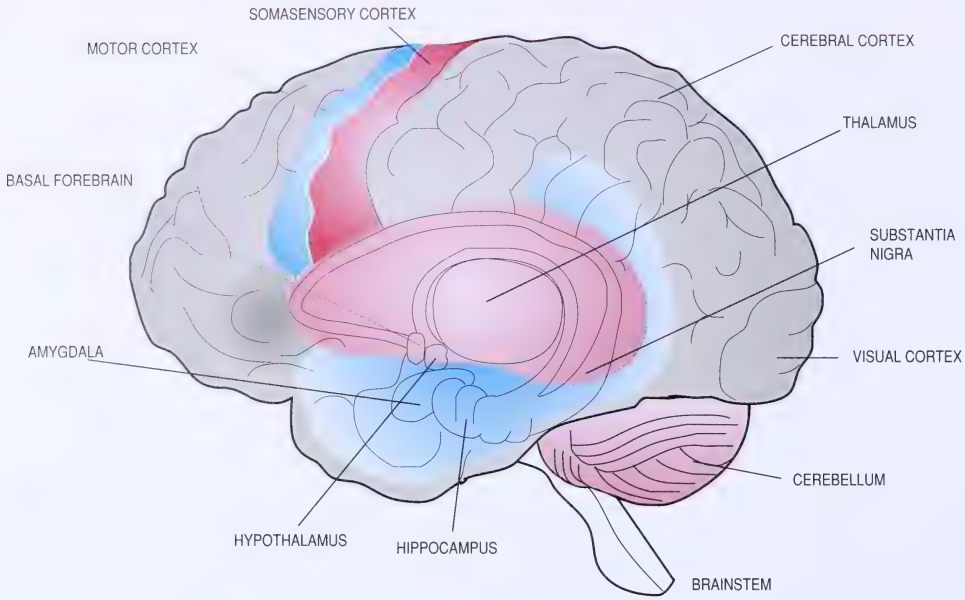
Dr. Witkowski also devised a custom-made Body Surface Mapping system which monitors heart function at 117 sites on the chest instead of the 12 used in conventional ECG readings.



Five of Dr. Frank Witkowski's electrodes to record transmembrane currents in cardiac muscle are smaller than a fruit fly's eye. In this electron microscope photograph, the arrow indicates the electrodes embedded in epoxy. A conventional recording catheter is shown in the background.

POWER CENTRE

POWER CENTRE



IN THE HUMAN BODY, THE BRAIN IS THE FRONTIER OF ALL FRONTIERS. Medical researchers have declared this the Decade of the Brain because they are convinced they will understand its power.

What is the Brain?

It is a three-or four-pound lump of tissue that governs every thought from the trivial to ideas for a new concerto, a new computer or a new society, and controls every action to bring those thoughts to realization.

In this modest mass of tissue, there are 100 billion diverse nerve cells, about the same as the number of stars in the Milky Way. These neurons are intricately connected with one another in a grand architecture that transcends the minds trying to unravel it, an architecture that makes possible memory, vision, learning, thought and consciousness.

Neuroscientists assume that mental events can be correlated with the patterns of nerve impulses in the brain. They are using advanced technologies to analyze how neurons communicate with one another, how they are organized in networks and how these connections change with experience.

AHFMR neuroscientists focus on three main goals: functional mapping of the brain (learning which areas control different activities), understanding the way neurons talk to one another, and repairing damaged nerves.

Pioneer brain scientist, Santiago Ramon y Cajal, described nerve cells as "the mysterious butterflies of the soul, the beating of whose wings may some day – who knows? – clarify the secret of mental life."

The beating of the butterfly wings refers to the rapid electrical messages travelling from neuron to neuron taking in information, processing it and sending out information, all in unimaginably brief time – milliseconds. Action potentials of about 100 millivolts occur when positively charged sodium ions move from fluid surrounding the cell into the cell interior.

However, these action potentials cannot jump from the tail (axon) of one neuron to another across the space between (synapse). Neurons have chemical messengers to cross the gap. When the current approaches, chemicals called neurotransmitters are released, which bind to special receptors on the second cell and cause membrane changes that either excite the cell into activity or inhibit it. A single neuron integrates up to 100 synaptic inputs, and not in linear order. One neuron is a microcomputer in the great computer of the brain.

Molecule to Mind

Taken together, 50 or more neurotransmitters make up the biochemistry of the mind. Scientists are learning how dysfunctions of these chemicals lead to neurological diseases and mental illness. They have learned the gross facts: People with Parkinson's disease have a shortage of the neurotransmitter called dopamine, and Alzheimer's patients have a lack of acetylcholine. Schizophrenia, the most common and devastating mental illness, is apparently related to dopamine dysfunction. GABA is an important inhibitory transmitter and therefore relevant in epilepsy, which occurs when too many cells are excited at once.

Though still in the kindergarten of biochemistry, researchers have learned enough about neurotransmitters to make first-generation drugs for neurological diseases. For example, Valium and other anti-anxiety drugs enhance the action of GABA. Antidepressants enhance serotonin. Antipsychotic drugs antagonize dopamine, and while they alleviate hallucinations and muddled thinking, they produce abnormal physical movements. In daily life, nicotine and other "recreational" drugs alter our brain chemistry.

Now scientists are studying how these transmitters are regulated by other agents and where they bind on molecules.

In the human body, the brain is the frontier of all frontiers.

AHFMR DISCOVERIES

There is a revolutionary way to watch the brain at work without invading the body. It's called Magnetic Resonance Imaging (MRI) and it's helping surgeons locate tumors and epileptic lesions, physicians monitor multiple sclerosis, and researchers map the brain. Instead of radiation, used in CAT scans and PET scans, MRI uses a magnetic field and radio waves.

The same technology is used for Magnetic Resonance Spectroscopy, which reveals brain chemistry rather than simply picturing anatomy.

Dr. Peter Allan heads an MRI research team at the University of Alberta which is advancing the technology. His colleague, neurosurgeon Dr. Andrew Penn, is discovering how MRI can aid surgery for epilepsy and decision-making about therapies for post-stroke patients.

An AHFMR researcher at the University of Minnesota, Dr. Ravi Menon and his colleagues have pushed the boundaries of conventional MRI. With a more sensitive technique called "fast MRI," they can capture images as fast as a thought. For the first time in history, humans can watch another human think. When the subject is asked to imagine a scene, an area on the computer screen lights up. *(See page 27.)*

Understanding Alzheimer's Disease

Until recently, there was no clue as to why abnormal tissue, called plaques and tangles, accumulates in the brains of Alzheimer's patients, giving rise to devastating senility. It's now known that the plaques contain the beta-amyloid protein and that at least some Alzheimer's disease involves mutations of the gene that gives rise to the precursor of this protein. So far, nobody understands how the protein ravages minds.

Dr. Irma Parhad is one of the neuroscientists helping to sort out the genetic and molecular events in the disease.

Helping Alzheimer's Patients

The University of Calgary Dementia Clinic, founded by Dr. Parhad, is a centre for clinical trials of new drugs for Alzheimer's and a place where patients and their families can go for accurate diagnosis and counselling. Though there is no cure, Dr. Parhad emphasizes that much can be done to help manage the patients and much needs to be done to help relieve the caregivers' unrelenting burden.

Psychology student Corinna Andiel's conclusions have implications for the care of people with Alzheimer's disease. Her observations of institutionalized patients suggest that their wandering behavior is due to understimulation.

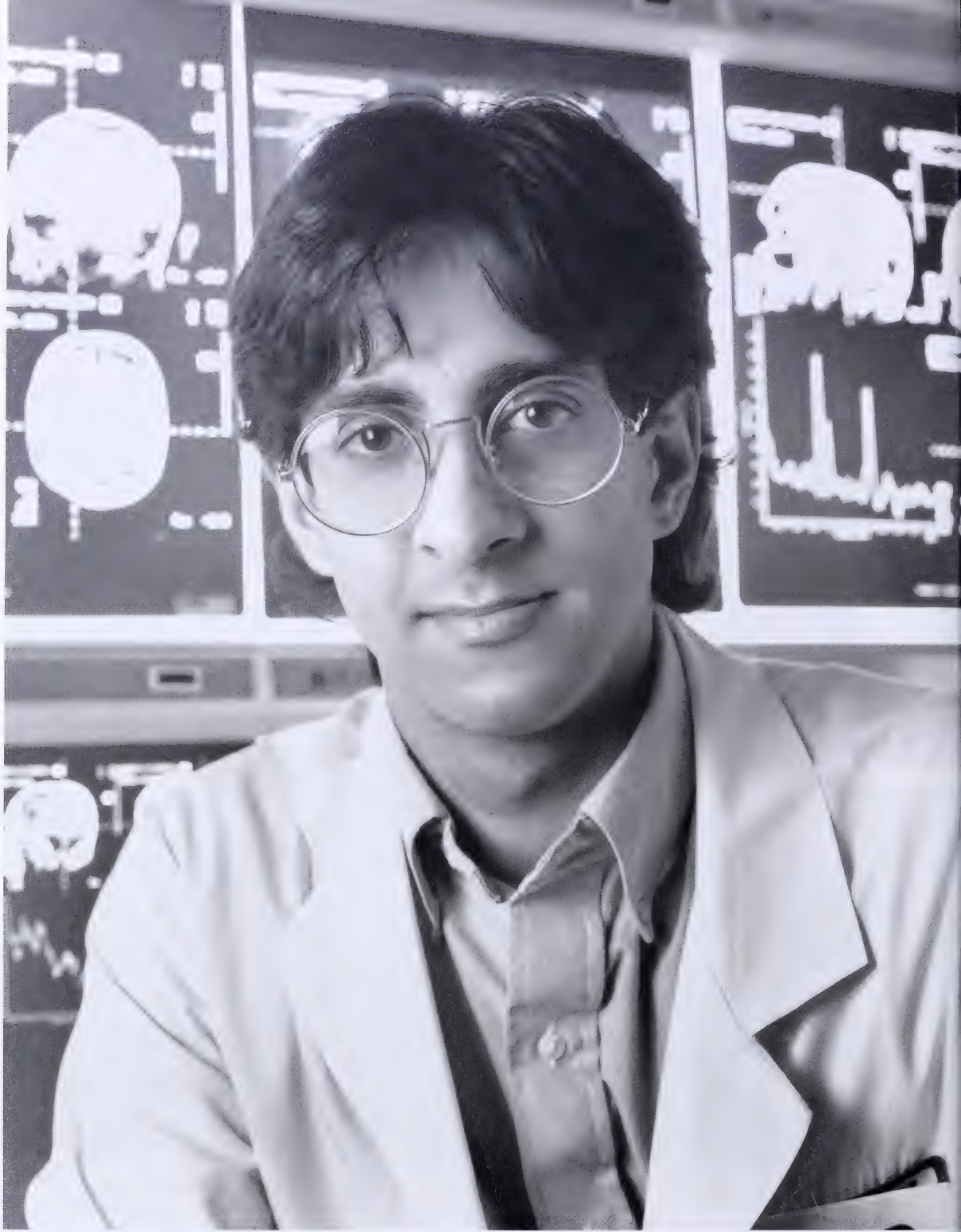
FIRST SCHIZOPHRENIA CHAIR IN NORTH AMERICA

Dr. Brian MacVicar holds the Ciba-Geigy Chair in Schizophrenia Research, the first of its kind in North America. Dr. MacVicar has won awards for his ground-breaking studies on the brain cells involved in epilepsy, research experience he is now applying to schizophrenia. Because the latest hypotheses point to altered pathways for several neurotransmitters, Dr. MacVicar is studying how these chemicals alter cells.

Dr. Brian MacVicar

POWER OF LOVE

George Miles is one of the Southern Albertans with Alzheimer's disease who receives up-to-date and compassionate care at the University of Calgary Dementia Clinic, founded by Dr. Irma Parhad. His wife, Jean, is also counselled at the Centre. Like other family members who care for a loved one with a chronic condition, Mrs. Miles demonstrates daily the healing power of love.



Dr. Ravi Menon

KEEPERS OF THE PROMISE:

WATCHING THE BRAIN THINK

DR. RAVI MENON IS A PHYSICIST WHO WATCHES THE BRAIN THINK. Sometimes it's his brain that his colleagues watch, as they each take a turn inside a large magnetic chamber.

Dr. Menon is a member of a hotshot team at the Centre for Magnetic Resonance Research at the University of Minnesota, that is pioneering an advanced system to literally watch the brain think.

The technology is called fast magnetic resonance functional imaging (MRI) and it's almost as fast as a thought. MRI is a way of imaging the brain using radio waves and magnetic fields instead of the X-rays used in conventional imaging methods such as Positron Emission Tomography (PET) scans. MRI has been used for almost a decade to locate tumors and brain damage in epilepsy or multiple sclerosis. One form of MRI, called spectroscopy, can also show how the brain functions by following the metabolism of molecules.

The Minnesota team now does something neuroscientists have long dreamed about – watching the brain think.

The team uses the new fast MRI to measure blood flow to activated neurons in the brain by following the oxygenated and de-oxygenated hemoglobin molecule, an idea developed by Dr. Seiji Ogawa of A.T.& T. Bell Laboratories. The principle is that blood flows to active areas of the brain, although scientists don't know why.

It is the imagining brain, seen for the first time in history.

At present, other methods are used to watch the brain at work – some of them invasive, such as attaching electrodes to brains during surgery or injecting radioactive dyes in PET scanning. Fast MRI is non-invasive – a researcher or volunteer lies inside the MRI chamber, which has a magnetic field 30,000 times more powerful than the earth's magnetic field. Subjects feel nothing as the magnetic field and radio waves cause atoms in the brain to emit signals, while the computer translates the action of the hemoglobin molecule into an image on the computer screen. Sometimes the subjects do a simple manual task and the motor area of the brain lights up.

Sometimes they are asked to imagine visually. "In your mind's eye, walk through your house and count the electrical outlets."

Then another area of the brain lights up, one never seen before. It is the imagining brain, seen for the first time in history.

Researchers have already made two-dimensional movies of the brain thinking by combining a series of rapid images. When computer technology catches up, they will make 3-D movies.

A physicist, Dr. Menon is responsible for writing the program which turns on all the technical items needed to do the imaging. He is also exploring why blood flows to activated neurons.

The excitement has brought Nobel Laureates and other distinguished scientists to the lab to see the action, and Dr. Menon is right in the middle of it.

Any Road Will Get You There

How does Ravi Menon find himself in a hot spot of brain imaging research? For starters, after his undergraduate degree, he studied MRI for seven years. AHFMR funded him for all seven, while he trained with MRI physicist Dr. Peter Allen at the U of A, whom Dr. Menon credits as an excellent mentor.

As he looks back, Dr. Menon says his early success comes from being goal-oriented and lucky.

"Traditionally, physics has always scared people away. When I graduated as an undergraduate from UBC there were four other people in my physics class at a university of 35,000. People think there are no jobs in physics, but it can be applied to everything. Just because you do an undergraduate degree in physics doesn't mean that you are stuck there.

"By my second year, I was interested in using physics for some benefit to mankind, as opposed to storing myself away in a lab studying some very small subatomic particle that might be interesting.

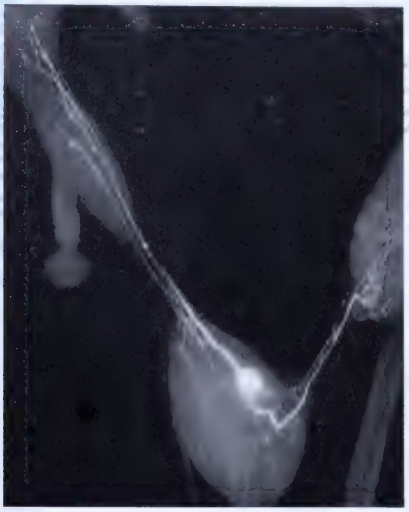
"Research is not just a matter of intelligence – we can't check people's brains with rapid MRI scanning and find answers. Progress is also a lot of luck and timing. I happened to be in the right place at the right time, which I guess is the way a lot of famous people start off. I think I have roughly the same amount of brain cells as anyone else, and luck really plays a part.

"Having a very clear focus is important too. I've always been very focused in terms of what I've wanted to do – use MRI to study the human body. I've been doing that for eight or nine years now."

"There's a Chinese saying, '*If you don't know where you are going, any road will take you there,*'" says Dr. Menon.

With him the truth is: *If you do know where you are going, every road will take you there.*

POWER LINES



This transplanted neuron is regrowing a connection to adjacent neurons.

THE BLINK OF AN EYE OR THE LEAP OF A BALLET DANCER depends on the neuron power lines reaching from the central computer, the brain, to every muscle in the body. Muscles move when they are stimulated by electrical currents from neurons. In paralysis, the power lines are either dead or broken. The same can be said for paralyzed or scrambled thoughts in diseases that deteriorate the brain.

In neuroscience labs across the country, there is a drama that shakes the very foundations of what we thought the human body was capable of, a kind of "coming back to life". It is the field of nerve regeneration – repairing the power lines, coaxing nerves damaged by accident or disease to come back to life.

Nerve regeneration is one of the themes of the national Network of Centres of Excellence, and AHFMR researchers in Edmonton and Calgary are prominent in the Network.

Finding ways to persuade injured nerve cells to come back to life.

The Impossible Becomes Possible

If you cut your finger badly, severing peripheral nerves, the body will gradually repair them so that your finger moves again, though perhaps stiffly and with some loss of feeling because the nerves have not reconnected precisely at their original position. The process by which the nerves grow back and their tails (axons) reconnect is called nerve regeneration.

Then why are people paralyzed?

The problem is that injured central nervous system (CNS) neurons, those in the brain and spinal cord, can't regenerate. No hope there. Well, that's what researchers agreed until the early 1980's.

Then a Canadian scientist, Dr. Albert Aguayo, showed that CNS nerves are capable of regenerating and restoring some function if they have an environment similar to the enviroment of peripheral nerves when they regrow. The impossible is now possible.

Rescue Molecules

AHFMR researchers and colleagues are busy identifying what is in the environment of a regenerating neuron. One of the key ingredients is nerve growth factor (NGF), and other substances are being discovered.

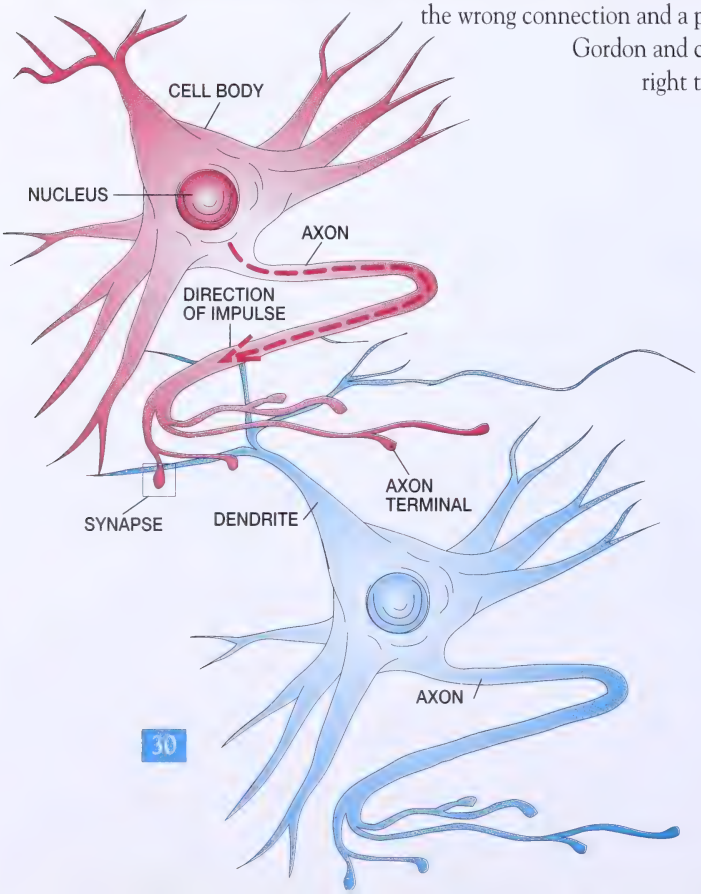
Perhaps these growth factors will be "rescue molecules" for people with paralysis or Alzheimer's disease, but the solution is not simply a matter of giving people NGF, though that is being tried for some conditions. There are complicated interactions to sort out, and many points to intervene. For example, too much NGF might initiate excess growth, leading to cancer.

To approach the problem, scientists first look for what normally controls NGF and other growth factors. For example, Schwann cells are involved, so perhaps this is a way of making the injured nerve cells more responsive to NGF produced by Schwann cells after injury, instead of directly loading on more NGF.

Before reliable therapies can be designed, all of the complicated interactions among nerve cells must be figured out – and remember, each nerve cell has 20,000 or 30,000 connections with other nerve cells!

The Right Hook-ups

Getting CNS or peripheral nerves to regrow is only half the battle. The other half is getting the nerves to reattach to the right target. The target might be another neuron damaged after a stroke or a disease such as Alzheimer's, or an injured muscle cell. This means understanding the blueprints of those power wires. Make the wrong connection and a patient could be worse off. AHFMR scientist Dr. Tessa Gordon and colleagues are studying how nerve cells recognize the right target under normal conditions and after injury.



A neuron that has been excited conveys information to other neurons by generating impulses called action potentials. The impulses travel down the axon and are converted to chemical signals at synapses, the contact point between neurons.

Mr. Kristian Vicei

"If you have the motivation and energy, you can do just about anything. I've told myself that the day I can climb my favourite mountain in B.C., I'll quit rehab," says Kris Vicei.

A former pilot and athlete, Mr. Vicei is paralyzed from the mid-chest down because of a motorcycle accident. He is determined to walk again with the help of therapy pioneered by Dr. Brian Andrews. The therapy combines electrical stimulation of paralyzed muscles and an innovative bracing system.

Therapy for the Paralyzed

An AHFMR team at the University of Alberta is one of the world's premier centres for electrical stimulation therapy, an idea that goes back 2000 years. (In 46 A.D. headache sufferers were promised relief if they put an electric fish on their forehead.)

Today, the working principle is this: Give paralyzed muscles small electrical currents to replace the natural currents lost through severed nerves. Sophisticated electrophysiological equipment allows researchers to apply electrical stimulation on the surface of the skin, or through electrodes implanted in the body.

AHFMR researchers have pioneered such therapy for stroke patients and spinal cord-injured patients. In ground-breaking experiments, they have given these people increased mobility, and muscles which normally would atrophy from disuse also maintain strength because of the stimulation.

Is nerve regeneration research on the way to miracles, helping the paralyzed to rise up and walk and the demented to come back to the land of logic?

Nobody can promise that, and certainly if any part of such an ideal scenario were to become true, it would not likely be for decades. Yet the possibility for bringing damaged nerves back to life is there, and this keeps neuroscientists slaving away at their parts in the great drama.

Helping the Paralyzed Move

WORLD FIRST

Dr. Arthur Prochazka and Dr. Richard Stein were the first in the world to develop electrical stimulation therapy for a stroke patient to use at home for increased mobility.

An industrial company is now working with the team on an advanced system for spinal cord patients, using implanted electrodes and pacemaker-like stimulators.

The University of Alberta team is also developing a system to control tremors in people who have multiple sclerosis or other diseases.

Secrets of Snails

WORLD FIRST

Dr. Naweed Syed set the neuroscience world back on its heels with discoveries about the neural control of one of the bases of life – breathing. He found the three master cells that control breathing in a common pond snail. At one point, he transplanted the cells back into the dying animal. It revived and behaved normally.

In his latest research, he has new information on how damaged nerves reconnect to the appropriate target by the release of neurotransmitters. (*See page 34.*)

Back to the Beginning

Dr. Freda Miller is one of the developmental biologists who look for clues in the embryonic stages of life to understand the factors that control rapidly growing nerve cells. She has shown that, in rats, some genes which are normally active only during development are re-activated after injury to promote regeneration. Protein products of these genes are candidates for new treatments in injury and disease.

Secret of Consciousness?

As you read this, you are an alchemist. In a millisecond, 125 million rod and cone cells in your retina are gathering light from this page. You are turning light into an electrical impulse that travels along the power lines to the brain where it is magically processed to make sense of the world you see.

Many people claim that it is impossible to divide the process of seeing from understanding, to separate acquisition of visual knowledge from consciousness. Perhaps that is why the visual cortex is the most studied and best understood part of the brain.

A team of AHFMR researchers at the University of Calgary is studying the visual process. For example, if Dr. Larry Haynes can discover how rods and cones adapt to different amounts of light, he will have insight into some retinal disorders.

Power Hearing

WORLD FIRST

AHFMR neuroscientists' discoveries about hearing have had immediate patient benefits.

One of the goals in medicine is to diagnose hearing problems accurately in infants so early therapy can aid normal speech development. Dr. Jos Eggermont's electrophysiology studies have led to better hearing tests for tiny infants. Other researchers use his expertise for testing and improving the cochlear implants which restore partial hearing for some deaf people.

His latest findings may help explain the mysterious and torturous disease, tinnitus. With tinnitus, people hear buzzing, ringing, roaring or other sounds that aren't there.

Dr. Eggermont's colleague, Dr. Barry Kimberley, has developed a portable, inexpensive test to screen hearing problems in schools, hospitals and clinics. Unlike the expensive, laborious testing in sound labs, this test requires only a microphone and transmitter placed in the ear. Sounds coming out of the ear are recorded and processed by a personal computer. The test takes only 10 minutes.

When Sarah was born she had her hearing tested at the Alberta Children's Hospital by hearing specialist Dr. Stuart Coupland. He used new, sophisicated tests designed by Dr. Jos Eggermont, a Heritage researcher studying the development of hearing. The tests identify problems earlier than was previously possible so that therapy for very young children can begin when they are developing speech.

Fun with Nerve Cells

AS A CHILD IN PAKISTAN, NAWEED SYED ALWAYS TOOK HIS TOYS APART. When he was seven, he took apart an electronic toy. His mother said, "Why did you do that? You'll be sorry if you can't get it back together."

"Of course I can. It will be easy because somebody else already put it together in the first place," he replied.

As an adult, Dr. Syed has taken apart what nature put together so he can solve one of the basic mysteries in the human body – how the brain controls breathing to keep us alive. To do it, he studied a common pond snail and came up with some answers that set senior scientists in the neuroscience world back on their heels – they'd been looking for the same thing for decades – and earned Dr. Syed many honors.

He began his ground-breaking research in Britain and continues it at the University of Calgary as an AHFMR researcher.

Tom, Dick and Harry

"I remember the first time I impaled a cell with a glass electrode, I just could not believe it. I had tears in my eyes sitting in front of an oscilloscope. It was really fascinating.

"I went home thinking, 'What if I never get that again! What if it's just a fluke.' At 2:30 in the morning I got up and went back to the lab to reassure myself I could do it again and again."

The story is typical of Syed's enthusiasm and determination, which partly explains why he succeeds where others failed. He talks with affection about the "beautiful" pond snails with neurons that partner or reject suitor neurons in the dynamic, microscopic world of the snail brain and culture dish.

The snail neurons are 100 times larger than vertebrate neurons, so they are useful for study. "You can see them so well, you can name them: Tom, Dick and Harry," explains Dr. Syed. Even so, some scientists told Dr. Syed he was crazy to try to figure out which of the pond snail's 6000 neurons controlled breathing. He was determined to do it.

He found three master cells that controlled the breathing process, then he hit an El Dorado of nerve cell studies. He made those three master cells function outside the snail's body in a culture dish just as they did in the intact creature.

Established scientists were impressed, but skeptical. How could he be sure the cells in the dish performed exactly as they did in the live snail where each neuron has many connections?

Dr. Syed moved his sleeping bag into the lab and emerged three months later with dramatic proof. He transplanted the cells back into the dying snail and it totally recovered. The snail had come back to life.

Dr. Syed's latest studies focus on learning how neurons choose or reject other neurons as partners before and after injury. The key to recovery from nerve injury or disease depends on the complicated circuitry of billions of nerve cells being rewired appropriately. Dr. Syed has evidence that the "marriage" of neurons is controlled by chemical signals called neurotransmitters.

Dr. Syed uses various approaches to study the nerve regeneration process, as competitive a field as his earlier studies. His ability to see problems from different angles – close-up and in an over-all picture – keeps him tuned to the central "logic" of biological processes, whereas some neuroscientists seem to get lost in the fascinating detail.

"My basic theme is to have fun and I've always been an explorer."

Perhaps the real secret of his success has to do with the little boy who took apart his toys for fun.

"My basic theme is to have fun and I've always been an explorer. If you don't have fun doing something, if you are very narrow-minded and always concerned about publishing, getting funded, and not perishing, the pressures can deter your ability to explore.

"I don't want to confine myself. I'm like a kid in the candy store, looking for the right candy. I think this is the right mechanism for nerve regeneration and I think it is a universal phenomenon."

Chances are, the neuroscience world will once again applaud the Syed kid having fun in a Calgary lab.

POWER START:

TAKING CARE OF BABY

RESEARCHERS ARE LEARNING HOW WE CAN TAKE BETTER CARE OF BABIES, especially those who rush into the world ahead of time and start life weighing less than a small sack of sugar.

"We want every baby to have the best start in life it can," says Dr. David Olson, Head of the Perinatal Research Centre at the University of Alberta. Dr. Olson was recruited from the University of Western Ontario to establish the Centre and continue his own studies on premature labor.

At the Centre, 27 researchers from medicine, rehabilitation medicine and nursing study why babies are born prematurely and how their early birth affects them and their families. The team of basic scientists and clinical researchers brings an integrated approach to the problems of pregnancy, fetal development, birth and newborns.

Advancing Women's Health

As in other areas of medical research, advances in genetics, molecular biology, and immunology are helping to answer questions about normal and abnormal pregnancies and births. But new research tools are not the main reason this is an expanding field. It's more a case of social trends. Women's health issues are being newly recognized, understood, and advocated by well-established women who are having pregnancies later in life.

Finding better ways to care for babies is effective preventive medicine because, obviously, healthier babies mean healthier children and healthier adults.

The New Issues

New technology can often save babies who have a little over half the normal time in the womb, but the majority will have long-term chronic illness or developmental handicaps. Dr. Olson stresses that babies who used to die, now live, presenting new medical challenges.

"So our specialty is evolving new definitions of health for these people, and society needs to wake up and realize it will be supporting them for the rest of their lives. We need to develop resources to prevent, or at least manage, the problems effectively.

"If we can learn to understand normal and abnormal fetal development, we can intervene when it is appropriate to minimize problems. If we understand the basic nature of the process, we might be able to buy more time for the baby to grow naturally inside Mother."

In addition to research activities, Dr. Olson and his colleagues actively promote education of the public and health caregivers with conferences and public lectures on such topics as "Exercise During Pregnancy" and "High Blood Pressure During Pregnancy."

AHFMR DISCOVERIES

Preventing Premature Birth

The majority of illnesses and deaths in infants is caused by preterm birth. Why are some babies in such a hurry to be born? Nobody knows, but Dr. Olson has some new clues about the onset of labor. He has found that a key enzyme is more active before both term and preterm births, and he has identified factors that increase the enzyme's activity. Eventually, such information might lead to new ways to prevent premature labor.

Helping Infants Breathe

Lung failure used to be the leading cause of death of preterm babies, but a new development called artificial surfactant has changed that.

Preterm babies with underdeveloped lungs lack surfactant, the substance that lines airways and alveoli, the sac-like working units of the lung. Without this lining, the sacs stick together and infants can't breathe.

Neonatal care has been revolutionized by the advent of artificial surfactant, a development aided by Dr. Samuel Schürch, who studies its surface properties. The companies who developed the artificial surfactants enlisted his aid to test them with his special mechanical model of alveoli. He also helped neonatal physicians at the Foothills Hospital test the benefits of the new surfactants on newborns.

When preterm babies must be put on the respirator and given massive amounts of oxygen, their lungs are sometimes permanently damaged. In animal studies, Dr. David Olson has identified some lung factors altered in oxygen-related damage, information that could be used to prevent the damage.

Understanding Crib Death

The sudden, mysterious death of a seemingly healthy infant from SIDS (Sudden Infant Death Syndrome) is a heart-wrenching tragedy. Apparently, the children die from heart or lung failure, but nobody knows the cause. There is no way to prevent SIDS or to know which babies are at risk.

Many researchers suspect SIDS can be traced to sleep patterns and a faulty arousal mechanism that wakes a healthy baby during sleep in brief periods when breathing stops, called apnea. Dr. James Fewell's animal research gives evidence that such a faulty arousal response is involved. He has also shown that this waking response in animals changes in the first three weeks after birth in active sleep, but not quiet sleep.

Underdeveloped regions of the brain that control breathing could be the underlying cause of SIDS. Dr. John Greer's innovative rat model allows him to study neural control of breathing before and after birth. Dr. Naweed Syed's studies on the neural control of breathing in the snail *(see page 34)* could also shed light on SIDS.

Better Infant Nutrition

WORLD FIRST

Dr. Johny Van Aerde, a neonatal physician at the University of Alberta Hospitals, developed an infant formula for preterm babies which gives them a better chance of developing normally and prevents a liver disease common to these vulnerable newborns. The formula is based on his studies of the fatty acids the infants need to grow and develop. Previously, they were given formula adapted from IV emulsions designed for critically ill adults.

Preventing Birth Defects

WORLD FIRST

If an unborn child carries abnormal chromosomes and the baby survives, it will have birth defects and varying degrees of mental retardation. Down's syndrome is the most common chromosomal disorder.

Dr. Renee Martin has discovered that many men have almost no risk of producing a chromosomally imbalanced child, while others are greatly at risk because three quarters of their sperm are abnormal. She also found that radiation therapy for some cancers increases abnormalities, as does aging.

This kind of information is critical for counselling couples who are considering having children, and Dr. Martin is the first to make such information available. That's because she pioneered techniques for activating human sperm chromosomes and determining if they are normal or not. Researchers around the world have adopted her methods for studying the origin of birth defects.

THE MOST POWERFUL DOCTOR IN THE WORLD

The Most POWERFUL DOCTOR in the World

THE MOST POWERFUL DOCTOR IN THE WORLD IS YOUR IMMUNE SYSTEM. This is true for almost all of us.

Every moment of our lives, our immune cells are defending us against millions of bacteria, viruses, tumor cells, parasites and other disease-producing agents. A trillion specialized immune cells work in a defense system that almost rivals the brain and nervous system in complexity.

Usually our immune system saves us, but sometimes it ruins us. When it malfunctions, it can unleash a torrent of diseases, from asthma to arthritis to cancer to AIDS. It can also reject life-saving organ transplants.

If there are revolutions in medicine, one of them is the immunology approach. On all fronts, scientists are discovering how the masterful immune system functions or fails, and they are beginning to design ways to boost it with immunotherapy.

An Impressive Army

The immune system must do four things: recognize the enemy, marshall defenses, mount the attack, and halt the action when the enemy is defeated. The three main types of immune cells – macrophages, B cells and T cells – communicate with each other by direct contact or by releasing chemicals called lymphokines or cytokines. The interleukins and tumor necrosis factor are among the best known lymphokines.

Consider the wonder of antibodies, released by the B cells. Within a few hours or days of infection by a bacterium or virus, B cells produce antibodies to fight it.

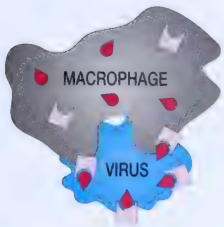
Amazingly, each B cell is designed for a specific target antigen, and soon after we are born, we have the ability to make antibodies for all the harmful agents we are likely to encounter over a lifetime – millions of them.

Antigens are any proteins that stimulate an immune response, and each antibody is designed to hook onto one antigen and no other molecules in the body. An antigen might be a protein on a virus, a bacterium, a parasite or a tumor cell. B cells either neutralize antigens directly or, indirectly, make enemy cells vulnerable to other immune cells.

Continued on page 42

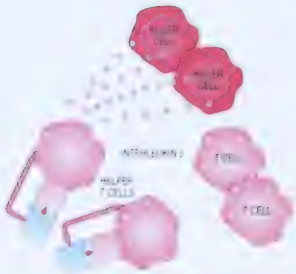
How It Works:

Suppose you have become infected with a cold virus.



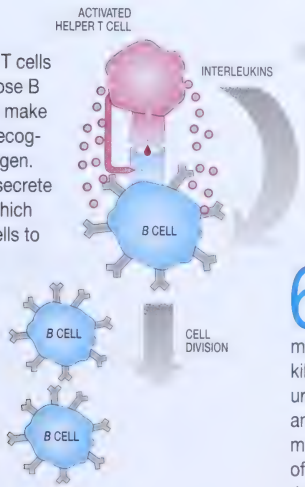
1 A scavenger macrophage will eat the virus and display the viral antigens on its own surface so the helper T cells programmed to read that antigen can see it.

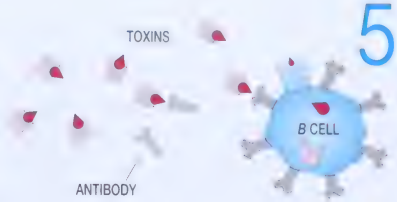
2 The macrophage calls the helper T cells into action by releasing interleukin 1 and other cytokines.



3 The activated helper cells produce interleukin 2, a call to other helper and killer T-cells to grow and divide.

4 The helper T cells activate those B cells which make antibodies that recognize the viral antigen. The T cells also secrete growth factors which cause these B cells to multiply.





5 T cell cytokines signal the activated B cells to secrete large amounts of antibodies to hook on to the antigens on the virus.

6 Helper T cells produce gamma interferon which has many effects: it activates killer T cells to attack, urges B cells to make antibodies, and keeps macrophages at the site of the infection and helps them digest the cells they have engulfed.

7 With each exchange of chemical signals, the immune response mounts until the enemy is overwhelmed.

If you have been vaccinated against the virus or infected with it before, the antibodies in your blood would eliminate the virus so fast, you wouldn't know you had been infected.

On the other hand, a virus may seriously weaken your immune system so it responds ineffectively or too slowly. The most notorious example is the HIV-1 virus, which destroys a class of helper cells called CD4 cells. A more controversial example is the Epstein Barr virus, which has been associated with chronic fatigue syndrome.

Boss Cells

T cells are the bosses of the immune system, regulating most of its functions. Helper T cells activate almost all the other T cells by releasing their chemical messengers. Cytotoxic T cells destroy cells infected by viruses or cancer, and they reject transplanted tissue or organs. Before they are activated to kill, they must first recognize a foreign antigen. Natural killer T cells are also lethal, but they can sidle up to a target tumor cell and give it the kiss of death, without having seen a foreign antigen.

Macrophages are scavengers which rid the body of worn-out cells and stimulate the immune response. A macrophage digests and processes antigen, then presents it to a T cell which can then see it is an enemy.

Once the immune response is complete, suppressor immune cells shut off the action. If they don't, inappropriate cells will be destroyed, and disease results.

Why does the body attack itself?

Self-Destruction: Autoimmune Diseases

Obviously, the immune system must be able to tell whether a cell belongs to your own body or whether it is foreign and dangerous. This is called distinguishing self from non-self. Researchers the world over are trying to learn how the healthy immune cells do this, because sometimes they make errors and attack the body's own healthy cells.

This happens in diabetes (insulin-producing pancreatic cells are attacked), multiple sclerosis (the myelin sheath around nerves is destroyed), lupus (multiple organs and tissues are attacked), and other arthritic diseases.

Much of the research focuses on the T cell receptors, which must recognize a specific antigen on the invading enemy, then fit into it as a key fits into a lock to initiate the immune response. Researchers also study the antigens on the surfaces of cells to be destroyed. For example, sticky carbohydrates on cell surfaces are important signals. Other scientists study a complex of genes called MHC that encode for proteins which mark a cell as self. These genes determine which antigens an individual responds to, and how strongly.

There is also evidence linking autoimmune diseases with viral infections, possibly contracted years before a disease appears.

The Mind Supreme

The best doctor of all may be our mind.

Immunologists are finding new evidence to support what has always been known, that the mind and body are linked. For example, macrophages respond to chemical messengers from brain cells and from the so-called "stress hormone," cortisol.

Appropriate exercise, which relieves stress, enhances levels of interleukin 1 and interferon, but competitive athletes exercising excessively under stressful conditions have fewer T cells and possibly weakened immune systems.

NEW IMMUNOTHERAPIES

Every week, there is another news story on an experimental immunotherapy. Most of them involve giving laboratory animals or patients one or more of the chemical messengers (lymphokines) that immune cells naturally release to make the whole system work. The body only produces very small amounts of these lymphokines, so they were not available for research or therapy until researchers learned to make them in the lab, using recombinant DNA and monoclonal antibody technology.

EXPERIMENTAL IMMUNE THERAPIES

Immunotherapies show promise, but none of the treatments have moved out of restricted patient studies into larger studies or medical practice. That is because the results are positive but premature, and the treatments usually have side effects. Since the immune system is complicated and any one lymphokine can have several functions in different situations, nobody is certain of the total effect of tinkering with it.

Because immunotherapy is a totally new approach, based on the body's own doctor and the underlying disease processes, it offers hope for conditions where traditional treatments have been useless.

❖ CANCER: Interleukins, interferons, and tumor necrosis factor (TNF) have been given to cancer patients to boost the activity of immune cells. TNF can destroy some tumors, while gamma interferon spurs production of killer T cells. Many variations of lymphokine therapy have been tried, such as extracting a patient's own T cells and treating them with interleukin, then returning them to the patient. Sometimes T cells called tumor infiltrating cells (because they naturally appear in tumors as the disease progresses) are extracted, treated and multiplied in culture dishes, then returned to the patient.

Some results are encouraging, but there are also serious complications with toxicity.

❖ MULTIPLE SCLEROSIS: One study has shown that MS patients can be immunized, working on the same principle as vaccines for measles or other infections. Apparently, in MS patients, basic myelin protein and another protein trigger the immune system to attack its own myelin. If given cattle myelin orally to induce tolerance, some MS patients have fewer severe attacks of the disease and there are no side effects. Other studies show beta interferon reduces MS episodes for some people in the early stages, although how it alters the autoimmune attack is not precisely known.

❖ ARTHRITIS: Cyclosporin is the wonder drug largely responsible for the high success rate of heart, kidney, and other transplants because it suppresses the immune system to prevent rejection. Cyclosporin has been tried for arthritis, with very limited success and severe side effects.

❖ DIABETES: Partly because there are several rat and mouse models of diabetes, researchers have been able to investigate the autoimmune response in this disease more closely than in multiple sclerosis or arthritis. In diabetes, they have acquired knowledge of the self/non-self recognition process that fails in autoimmune diseases. Various studies in the last 10 years have experimented with cyclosporin, interferon, and other lymphokines to see if the self-attack can be halted or prevented.

DISCOVERIES BY AHFMR IMMUNOLOGISTS

WORLD FIRST

Activated killer T cells sidle up to a tumor cell (or a foreign, transplanted cell) and deliver a chemical letter bomb that blows up the tumor cell. Several years ago Dr. Chris Bleackley discovered a family of proteins in the bomb and he has since identified some of the genes which control the activity of these proteins.

He has also applied his findings to such medical problems as determining the immune response of the elderly to flu vaccines and development of a gene probe for kidney transplant rejection.

Dr. Chris Bleackley

❖ Dr. John Reynolds' studies on B cells could help explain autoimmunity or lead to a new therapy for cancer. He has new information about why and how the body produces masses of B cells, only to destroy them eight hours later in a process called programmed cell death or cell suicide. He has shown that the B cells produced in intestinal lymph cells commit suicide by activating an enzyme that fragments their DNA. If he can develop a monoclonal antibody that recognizes cells targeted for destruction, it might be used to speed up tumor cell destruction.

Dr. Sandra Cockfield

Dr. Reynolds was awarded the Jessie Boden Lloyd Professorship of Immunology Research in 1992 to advance immunology studies at the University of Calgary.

❖ Dr. Sandra Cockfield, a kidney specialist, has identified the normal pattern of gene expression for interferon in mice. This kind of basic information on how interferons actually work is essential in developing more effective anti-rejection drugs for transplants.

❖ Dr. Kevin Kane has developed a new method to isolate molecules in the body which are presented with foreign antigens to the T cells so that they see they must mount an immune attack. Understanding these molecules can be directly applied to vaccine development.

❖ Dr. Paul Kubes' research could lead to new ways to prevent uncontrollable inflammation in joint and bowel diseases. In inflammation, white cells abnormally adhere to blood vessels. Dr. Kubes has shown that, under normal conditions, nitric oxide keeps white cells from sticking to vessels in animals, and blocking nitric oxide results in adherence of the cells.

ATTACKING ASTHMA

Dr. Dean Befus

Dr. Dean Befus heads the new Alberta Asthma Centre at the University of Alberta which is coordinating provincial research efforts to fight one of the most common chronic diseases in Canada. Asthma affects 1 in 10 children and it is on the rise. So are the death rates, and Alberta has the most asthma-related fatalities in the country.

About half of asthma cases can be traced to allergins such as house-dust mites and animal dander. For unknown reasons, the immune system responds to these harmless antigens as if they were harmful and sets off a heightened inflammatory response that blocks airways, causing coughing, wheezing, and breathing difficulties. Sometimes asthma can be triggered by a severe cold, which leaves viruses suspect. Exercise-induced asthma is triggered by physical activity. Heredity is another factor researchers are exploring.

Many drugs have been used to reduce airway inflammation in asthma, some of the newer, stronger ones being most controversial because of potentially serious side effects. The problem is that if a drug reduces airway inflammation, it may also shut down critical immune defenses in other parts of the body.

The newest approach is to understand the underlying causes of asthma by looking at the immune cells and the chemical signals that control the inflammation in healthy people and in asthmatics.

Dr. Befus is investigating how one class of asthma drugs, beta-2 agonists, affect mast cells. These cells release the chemicals that create asthmatic symptoms.

Dr. Dale Lien has new information on the role of neutrophil cells in airway inflammation.

AHFMR funded Dr. Donald Enarson and colleagues to survey lung disease in Wetaskiwin and Camrose farmers. The team found some reduction in lung function, but no more disease than in the control group of Drayton Valley outside workers. A sub-group of farmers had asthma caused by grain dust.

ALLERGIES

The topic of food allergies makes for heated arguments. Some people have them, or think they have them, and physicians try to sort out the difference. Dr. Brent Scott finds himself right in the middle of the controversy. A gastrointestinal specialist, he cares for children with allergies and other digestive problems at the Alberta Children's Hospital. In the lab he is finding out precisely how the digestive system responds in allergic reactions to food proteins or bacteria which cause diarrhea.

Medically speaking, physicians consider that a food allergy occurs if the immune system is involved in the adverse reaction. The antibody IgE, which is attached to mast cells in the body, binds to ingested food proteins. This causes the mast cells to release chemicals which create the symptoms: watery eyes, swelling, breathing problems, diarrhea. If the immune system is not involved, but there are still symptoms, researchers call it a food intolerance.

In the Body or the Mind?

Dr. Scott stresses that allergies are complicated and other biological mechanisms can cause either food allergies or intolerance. Then there is the body-mind connection. Both animals and people can be conditioned to the allergic response. If someone has not eaten a supposed allergy-triggering food, but he thinks he has, the allergic symptoms sometimes appear.

Dr. Scott explains, "Nerves can stimulate mast cells to degranulate as part of learned response to repeated exposure to a food, and when mast cells degranulate, they send messages to nerves, so it's an interactive system."

His basic studies have shown that the bodily response to food antigens is complex, with direct and indirect effects on the small intestine, and with different effects on the stomach. By identifying the body chemicals that mediate allergic responses, he has new leads on some drugs that might block them.

"Mom, My Stomach Hurts"

The majority of the 1600 children Dr. Scott and his colleagues care for as outpatients of the Alberta Children's Hospital do not have allergies, but some form of inflammatory bowel disease – failure to thrive, chronic or acute diarrhea, and most commonly, abdominal pain or constipation. Twelve percent of all girls and ten percent of all boys have unexplained stomach aches.

"The vast majority of people with abdominal pain don't have a real disease, but they have a real complaint, with varying degrees of trouble managing it. We see a whole spectrum of people, and care involves identifying those with disease and those with 'functional' pain," explains Dr. Scott.

"Functional pain is very real in the sense that it hurts just like a headache. Most of them are very well kids, but there's a whole iceberg there. Sometimes their discomfort is associated with their personality and environment, and how they deal with stress. Our brain and emotions influence whether or not we experience abdominal cramps. Also, disorders such as milk sugar intolerance can produce pain in the absence of disease. "Some people do exceptionally well once you explain the problem to them, while others need ongoing care and support."

Eleven-year-old Heidi Sheppard isn't worried about her chronic stomach aches any more. Dr. Brent Scott was able to diagnose the cause (colitis) and prescribe effective treatment to control them.

This is part of the specialized care Dr. Scott gives to children with allergies and gastrointestinal problems at an outpatient clinic at the Alberta Children's Hospital.

POWER OF PREVENTION:

NEW VACCINES

THE BEST MEDICINE DOESN'T FIX PROBLEMS: IT PREVENTS THEM. In the history of medical research, vaccines represent a major triumph, largely wiping out diphtheria, polio and other major infections.

Many AHFMR researchers are on the leading edge of vaccine development for whooping cough, meningitis, and diseases we don't normally associate with vaccines – cancer and diabetes. The new molecular biology tools allow researchers to engineer safer, more effective vaccines or entirely new ones. The key ingredient in a vaccine is the antigen that stimulates the immune response. Essentially, the immune T cells spy a foreign protein (antigen) and other immune cells make antibodies to it. These antibodies remain in the blood to fight subsequent infections. Also, the next time the immune cells see a similar antigen in a related infection, they remember what they've learned and call forth the same antibodies.

In the past, vaccines were made by killing the whole virus or bacteria, or choosing a live but harmless strain. Sometimes the vaccines were not so harmless. With genetic engineering, researchers can now identify which part of the organism stimulates the immune response and isolate only that part, leaving behind the parts that cause toxicity. Or researchers can chemically synthesize the antigen and assemble variations of it. Desired antigens are mass-produced with DNA technology so that vaccines are more affordable.

By studying the structure of molecules, protein chemists can design vaccines based on the interaction between surface antigens and immune cells.

Leads on a Malaria Vaccine

When Dr. John Elliott and his family visited a refugee camp in Thailand, he watched his 18-month-old daughter sleeping under a mosquito net. Would a malaria-carrying mosquito bite her? Surely some of the children in the camp carried the disease.

The experience made him even more determined to find an effective vaccine against this scourge. About 1.5 million people die of malaria every year, and another 300 million are infected.

There is evidence that antigens found on the surface of the malaria parasite could be useful for vaccines. Dr. Elliott uses a new method of gene cloning, called eukaryotic expression, together with antibodies from people who are immune to malaria, to find new malaria genes which make parasite surface antigens. He has identified several that could be useful either at the blood stage or the insect stage of the most deadly form of malaria.

U of C researcher Dr. May Ho spends time in Thailand studying the interactions between malaria parasites and their human hosts. Some of these interactions lead to immunity in people who will not be reinfected, and others leave people vulnerable to malaria. Such information about protective T cell responses assists vaccine development.

Better Meningitis Vaccine

Canadians have been frightened by recent meningitis outbreaks among teenagers. Although there are effective vaccines against the most common type of meningitis, the vaccine for Neisseria meningitis is less than satisfactory.

Fortunately, Dr. Tony Schryvers' experimental vaccine works well in animals. It is based on the fact that the bacteria need iron from the host to survive, so blocking their iron receptors destroys them. The next step is to determine whether the vaccine will stimulate an appropriate response in all the sub-types of this bacteria.

Dr. Schryvers has received almost a million dollars in industry funding to pursue his vaccine research for several bacterial infections.

Dr. Tony Schryvers

Whooping Cough

The current vaccine for whooping cough has been a matter of controversy, since it was, according to most researchers, falsely accused of being inordinately dangerous to the nervous system, a matter that reached the law courts. When some parents refused to have their children immunized, alarming outbreaks occurred.

Dr. Randy Read and his colleague, Dr. Penny Stein, have begun to identify the structure of the pertussis toxin. They've done it using X-ray crystallography. X-rays directed through pure crystals of a molecule are scattered in a pattern according to the location of atoms. This pattern is translated into a 3-D image of the molecule's structure on a computer screen. It may take years to develop the whole structure, but even a partial one can help chemists design a vaccine.

Cancer Vaccines

Edmonton-based Biomira, one of Canada's leading biotechnology companies, is working towards cancer vaccines. The vaccines are based on the fact that some cancer cells have unique surface antigens, not found on the surfaces of healthy cells or other cancer cells. The strategy is to synthesize these specialized antigens, attach them to a carrier protein which further stimulates the immune system, then give them to cancer patients in the hopes of stimulating antibody production and other immune activity against the cancer cells.

AHFMR gave Biomira repayable Technology Commercialization funding for clinical trials of the experimental vaccines.

(For information on a potential vaccine for diabetes see page 52.)

POWER STRUGGLE:

DEFEATING DIABETES

Left to right: Dr. Norman Kneteman, Dr. Garth Warnock, and Dr. Ray Rajotte

THOSE OF US NOT AFFLICTED WITH DIABETES tend to think that the heralded Canadian discovery of insulin and the development of insulin therapy solved the problems. Unfortunately, not so. Despite insulin replacement, more than 50,000 Canadians with insulin-dependent diabetes are at risk for serious complications, including kidney and heart failure, strokes, blindness and peripheral nerve damage.

The good news is that researchers are on the edge of triumph in the long power struggle with the disease and on several fronts AHFMR researchers are leading the way.

WORLD FIRST

Free of Insulin Therapy!

Edmontonian Marge Heayn and the University of Alberta islet transplant team have made world history. Mrs. Heayn had suffered from severe diabetes for 26 years. In conjunction with a kidney transplant in 1990, the U of A team transplanted healthy insulin-producing islets into her liver. The happy islets produce natural insulin and for more than two years Mrs. Heayn was free of insulin therapy.

Mrs. Marge Heayn made world history when she became the first person with insulin-dependent diabetes to go off insulin therapy for more than two years. It was possible because a team of AHFMR researchers transplanted healthy insulin-producing cells into her.

"Before my transplants, life was very wearing . . . but now I feel positive about life," says Mrs. Heayn.

In late 1992, she went back on insulin because of complications with drugs taken to control rejection responses to the transplanted kidney. However, the islets continue to function well, and when her other problems are under control, it is anticipated that the insulin therapy will be halted again.

The success was the combination of years of work by team members Dr. Garth Warnock, Dr. Norman Kneteman and Dr. Ray Rajotte.

It was also payoff in the AHFMR's investment in three bright researchers who grew up in rural Alberta to become scientists at the U of A. Dr. Rajotte, an expert in cryopreservation of cells for transplantation, helped train the two younger scientists, who were sent by the AHFMR to England and the United States to bring expertise from leading labs to Alberta. Dr. Warnock developed superior ways of harvesting donor islets and Dr. Kneteman worked on improving drug therapy to prevent rejection.

Now the rest of the world looks to this team for expertise.

Islet transplants are still experimental and limited to selected subjects who are receiving kidney transplants, but the promise of finally being able to correct the basic problem in Type I diabetes through transplantation remains golden.

Thanks to this pioneer research, someday children who show early signs of the disease could receive islets before any complications occur.

Potential for Immunotherapy

Diabetes researchers are busy figuring out why the body's immune system destroys its own insulin-producing beta cells in the pancreas. What antigen triggers this autoimmunity? After the initial signal, how do all the different immune cells respond to complete the destruction?

If this can be understood, new immunotherapies could be devised to alter the process.

Dr. Alex Rabinovitch and other researchers have evidence that certain lymphokines produced by the immune cells are key to the destruction process. In animals and cell culture, they are experimenting with "lymphokine cocktails" to see if they will make a difference.

Dr. John Elliott is studying antigens found only on the surface of beta cells. These antigens may trigger the autoimmunity and one called GAD could help predict who will develop Type I diabetes.

Dr. Ji-Won Yoon has discovered that certain autoantigens appear in animal models of diabetes before symptoms develop, providing another possible lead in the cell destruction process. He also has evidence that viruses make susceptible people more susceptible to insulin-dependent diabetes. Researchers have long suspected an environmental trigger for some diabetes.

WORLD FIRST

A Vaccine for Diabetes?

By the time this report is published, there may be announcements about a new vaccine for diabetes, arising out of the work of Dr. Bhagirath Singh.

Dr. Singh, a pioneer in understanding immune cell responses, was an AHFMR scientist from 1985 to June of 1992, when he moved to the University of Western Ontario as new Chair of Immunology and Microbiology. While in Alberta, Dr. Singh discovered that a substance which formerly had been added to other, older vaccines prevented Type I diabetes in genetically susceptible mice.

The microbial antigens in this substance, called an adjuvant, somehow prevent the autoimmune response. Since then, Dr. Singh and other researchers have produced the same effect with a similar adjuvant that is safe for humans.

Dr. John Elliott, AHFMR researcher at the U of A, collaborates with Dr. Singh in identifying the antigens responsible for the effect.

Drs. Elliott and Singh are also working with the islet transplant team to determine how the vaccine prevents autoimmune rejection of transplanted islets, thus avoiding a repeat performance of the autoimmunity that originally destroyed the natural islets.

Dr. Elliott cautions that even if clinical trials prove the vaccine works, there is still the big question of who should receive it, and when: before or after symptoms appear?

"A vaccine will probably not work for everybody," he adds.

Making Life Easier

Within a few years, some people with Type I diabetes may sport a new gadget that could save their lives, or at the very least make life easier.

It's an implanted insulin sensor that accurately monitors blood sugar levels. It could be connected to an implanted insulin pump that is turned on when an alarm signal from the sensor indicates that blood sugar is dangerously high or low.

The monitoring ability alone would simplify life for people with diabetes. Now they must suffer four or five pinpricks a day for tedious blood tests.

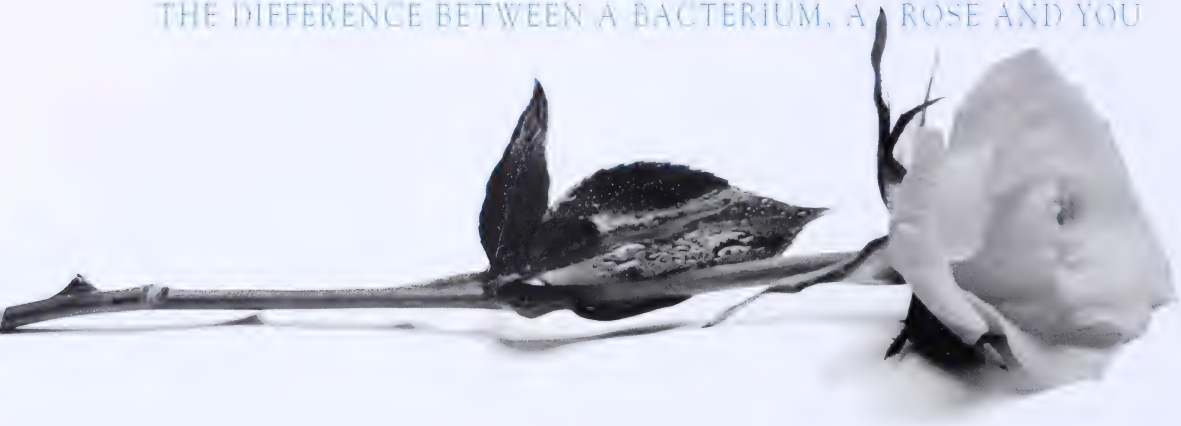
U of A medical engineer Dr. Francis Moussy developed the device, in collaboration with Dr. Ray Rajotte and chemist Dr. Jed Harrison. It works well in the lab situation, and preliminary tests indicate it is effective in animals.

The remaining question is: Will it remain biocompatible for a sufficient length of time? Past attempts by other researchers have failed the long-term biocompatibility test, but so far Dr. Moussy's device works well in animals.

POWER OF THE GENE

POWER OF THE GENE:

THE DIFFERENCE BETWEEN A BACTERIUM, A ROSE AND YOU



WHAT MAKES A ROSE A ROSE? The same thing that makes you, you: Genes.

About 100,000 genes linked together in the structure called DNA inside your 60 trillion cells determine all your body characteristics. Each cell in your body has enough genetic information to create another you. DNA (deoxyribonucleic acid) is the master molecule of life because it contains the blueprint for all life.

If all your DNA were strung together it would reach to the moon and back 8000 times!

In humans, DNA is organized into 23 pairs of chromosomes, one in each pair from the father and one from the mother. The DNA itself is made of building blocks called nucleotides bound together in a double helix. A gene is simply a specific section of the DNA molecule that contains the information to make a certain protein, according to the sequence of the base nucleotide pairs. There can be from 2000 to a million pairs in a gene. When a protein is made, scientists say the gene has been "expressed".

Only 3% of DNA codes for proteins. The purpose of the rest is not well known, but DNA must do other things – copy itself, transcribe or translate information in the genes and turn genes on and off. Many researchers are looking for the switches in these functions, because when they don't work properly, disease-causing mutations can result. For example, mistakes in copying DNA during cell division are one way a normal gene can become a cancer-causing gene.

Unravelled, your DNA would stretch to the moon and back 8000 times!

Genetic Disease

Understanding DNA is the greatest medical revolution in human history because it concerns the source of physical life.

Genes contribute to diseases in a variety of ways. What we normally think of as the classic inherited diseases, such as Huntington's disease or cystic fibrosis, are only part of the picture. These are called single-gene disorders because if you inherit the specific gene for them, you always get the disease.

Many other diseases are "genetic" because you can inherit a susceptibility to them. If you have certain susceptibility genes, you will get the disease if the environmental triggers are present. For example, viruses could trigger diabetes in people with an inherited predisposition to it.

Researchers are just uncovering such genetic predispositions, so far linked with Alzheimer's disease, cancer, emphysema, manic depression, schizophrenia, alcoholism, heart disease, and many other conditions.

Heredity plays a role in about 4,000 diseases.

AHFMR scientists are advancing knowledge about hereditary diseases. Accumulated information from researchers around the world is leading to new strategies to manage or prevent these conditions.

Strategies Against Genetic Disease

There are four main lines of attack in dealing with genetic diseases. First there is the race to identify which genes directly cause hereditary diseases or indirectly cause other diseases. The next step is developing diagnostic probes to screen those who carry the genes. Once they are identified, genetic counselling can influence prospective parents' decisions about having children at risk. As well, careful monitoring is possible to treat diseases in the earliest stages of development. Lastly, new treatments can be developed. Some are based on the consequences of the gene's behavior. For example, a new drug might be developed that blocks a protein expressed by a disease-causing gene.

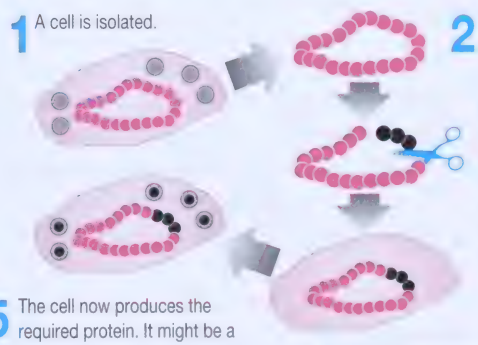
Then, there are the radical, controversial and exciting possibilities of gene therapy – altering or replacing faulty genes.

The Technology

Recombinant DNA technology is the basis for much medical research and its applications. Scientists use chemical scissors called restriction enzymes to cut DNA into specific segments and recombine them or insert a new set of genes with new instructions. Gene cloning – making thousands or millions of copies of an identical gene – uses this technology.

The fragment of DNA is inserted into the DNA of such one-cell organisms as bacteria, viruses or

RECOMBINANT DNA TECHNOLOGY


1 A cell is isolated.
2 Its DNA is removed.
3 The strand of DNA is cut with chemical scissors – naturally occurring restriction enzymes found in bacteria. There are over 400 of these enzymes.
4 A new set of genes with instructions on how to make a certain protein is inserted and placed back in the cell.
5 The cell now produces the required protein. It might be a missing protein to correct a disease. It might be a medically useful protein like insulin, in which case the DNA is extracted from bacteria. When the altered DNA is replaced, the rapidly multiplying bacteria become living factories to produce large amounts of the desired protein.

yeast, and cultured in the organism so that they produce the copies. A newer and more efficient method of cloning is called polymerase chain reaction.

Gene cloning of human insulin made it available to diabetics for the first time. Prior to that, there was no way of making the large amounts necessary, so animal insulin was prescribed. The ability to clone many other proteins naturally occurring in small amounts has revolutionized medical research.

Gene therapy may free some of us from the tyranny of heredity.

There are very few medical researchers who do not use DNA technology in some form. The technology is essential for studying the proteins which govern the molecular events in the body, developing drugs to compensate for faulty events, designing vaccines, or creating animal models of diseases, to name a few applications.

Recombinant DNA technologies allow scientists to make gene probes for diagnosing diseases and to learn what particular genes do. The probes are based on the fact that a single strand of DNA will bind to another strand if the sequence of the nucleotides is complementary. In other words, DNA sticks to like DNA. Then if you label it radioactively or biologically, you can see if a certain gene or specific mutations of it are present. A useful probe is only possible if the DNA sequence of a gene mutation causing a disease or a sequence near the mutation is known.

Even when researchers have identified the genes for a specific disease, they can often find markers associated with the disease. These are found through complicated analyses of large numbers of family members with and without the inherited disease. Other genetic diseases are diagnosed through chromosomal analysis (Down's Syndrome for example), by testing for the proteins expressed by maladaptive genes, or by measuring the biochemical effects of mutated genes.

In late 1992 and early 1993 scientists announced they had found genes responsible for ALS, myotonic muscular dystrophy, Huntington's disease and adrenoleukodystrophy.

New Territory

Geneticists are also finding that the old basic rules of inheritance handed down to us by the 19th century monk, Gregor Mendel, and memorized by every high school student, don't tell the whole story. Contrary to expectations, there are jumping genes that leap from one chromosome to another, expanding genes that work like accordions, and even proteins specified by genes that don't exist in the conventional sense!

Most tantalizing of all, there is evidence that organisms can respond to the environment by altering their genes!

The Human Genome Project

Medical researchers around the world have launched the largest single research project in history: mapping and sequencing all the genes which make up the complete library of our genes, called the human genome. It is also one of the most controversial projects. Some scientists claim it is our best hope for controlling disease. Others say the benefits are doubtful and do not justify the staggering costs. Sequencing the human genome requires $200 million a year for 15 or more years as well as international cooperation. Already there have been disputes over researchers who won't share their findings and court cases over who owns the rights to sequences with potential commercial value.

AHFMR researchers contribute data to the Human Genome Project.

The CF Story

The story of cystic fibrosis illustrates the promise and the present limitations of genetic research. In 1989, Dr. Lap-chee Tsui at the Hospital for Sick Children in Toronto and Dr. Francis Collins of the University of Michigan discovered the CF gene after studying the blood samples of more than 500 affected children. Subsequently, a test was developed to identify carriers, and a prenatal test was developed to show if a fetus is carrying the disease. Researchers have also identified more than 300 mutations of the CF gene. They have some insight into how the protein expressed by the gene alters chloride ion transport across the membrane of epithelial cells, which could account for many of the symptoms. Such information could lead to new drugs.

U of A researcher Dr. Malcolm King is part of an international team studying new therapies to promote chloride ion transport in cystic fibrosis.

It all sounds wonderful, but incomplete information may cause as much anxiety as ignorance. So far, there are some mutations which can't be detected, so although a negative screening test means there is a low risk of being a carrier for the disease, nobody knows for certain that the person is not a carrier. In March of 1993, more confusion was created when researchers showed that there are two variations of CF, a mild and a severe one. Doctors can tell which form an unborn child has, but not to what degree the disease will affect it. The positive side is that researchers suspect the mild form may respond to treatment that increases chloride ion movement from cells.

In January of 1993, University of Pennsylvania researchers announced they are initiating an attempt to use a cold virus, rendered harmless, to carry a healthy CF gene into patients' lungs. Researchers have already successfully transferred healthy, functioning CF genes into the lungs of rats.

Gene Therapy

The fall of 1992 marked the second anniversary of the world's first attempt to cure an illness with gene therapy. The illness was ADA deficiency and patients' lives hinged on the success of the therapy. Children born with a deficiency of the enzyme, adenosine deaminase, have virtually no immune defense. They are the "bubble" children who live in isolation inside a plastic bubble to keep out all germs. In 1990 a four-year-old girl with the disease was injected with white blood cells carrying a transplanted gene that makes ADA. The therapy worked.

This is gene therapy on somatic genes, those affecting an individual, but not his or her offspring. It still promises unprecedented control of diseases but at this stage the therapy is controversial because it's complex and bears risks as well as potential benefits. Altering germ line genes is even more controversial because this would affect offspring in unknown ways. Many scientists do not think the technology should ever extend that far. This is only one of the many ethical issues surrounding genetic screening and therapy.

As of 1992, there were gene therapy trials underway for ADA deficiency, advanced cancers including ovarian, skin, kidney, lung, and brain cancers, AIDS, hemophilia B, and hypercholesterolemia (a fatal excess of cholesterol).

The Ethical Questions

In genetic engineering, as elsewhere, science gives us new tools to do fantastic things, but it doesn't tell us whether we should use them or not. Thorny ethical issues plague medical research. Some scientists worry about them and they stress that the issues must be worked through by society, not only scientists. Meanwhile fearful, and not always well informed, public activists have tried to halt genetic research or screening programs.

Sorting out the issues and safeguarding everyone, while exploiting the technologies for better health, is an unprecedented challenge. Here are some of the questions to be answered:

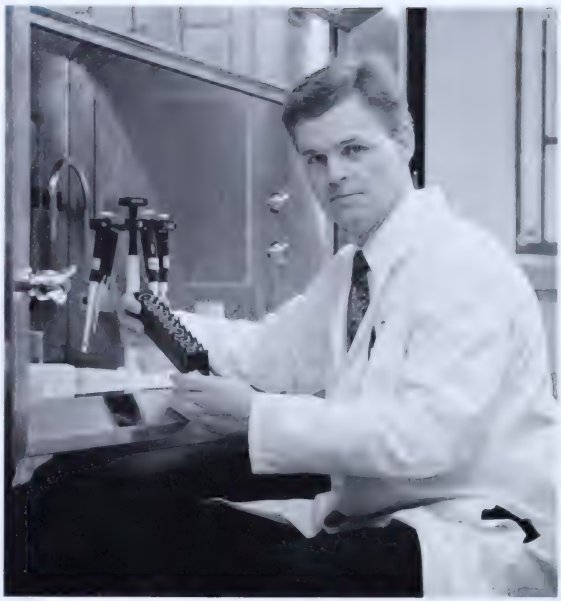
- Could genetic engineering go too far and become the avenue for "designer people" just as we create new animals, new plants, new medicines and other biotech products?
- How do we distinguish between trivial use, inappropriate use, and medically justifiable use?
- Could genetic knowledge be used to support claims of racial superiority or discrimination against individuals?
- Should people at risk for a devastating or fatal disease be informed of it if nothing can be done to prevent it or cure it?
- Should the results of genetic screening be made public to employers or insurance companies?
- Who pays for genetic screening?
- Should screening be voluntary or mandatory?
- How will genetic screening affect abortion issues?
- At what point is experimental gene therapy ethical?
- How do we educate people about such a complex area so they can make informed decisions?

How can we ensure that genetic information is not misused?

Multiple Sclerosis

For unknown reasons, Alberta has close to the highest incidence of multiple sclerosis in the world. MS is a mysterious disease in which the immune cells mistakenly attack the myelin sheath around nerves. Unlike cystic fibrosis, MS involves many genes, possibly 10, which confer susceptibility, not the disease itself. MHC genes, which code for self markers on the body, and some T cell receptor genes have been implicated because these genes are central to the way the immune system discriminates between its own body and foreign cells.

To identify MS genes, Dr. Robert Bell is studying the DNA of 200 Canadian families with children who have MS, but the parents do not.



Dr. Robert Bell

Juvenile Arthritis

We usually think of rheumatoid arthritis as a condition of the elderly but in fact one in 500 children has it. Dr. Walter Maksymowych has identified an association between a gene for a T cell receptor and the disease. The presence of the gene seems to predict whether a child's arthritis will progress to a more serious form. This is important information when physicians decide on appropriate drug therapy because, although arthritis drugs are potent, they can have severe side effects. Preliminary evidence shows a similar genetic link with adult rheumatoid arthritis.

As in MS, many genes are likely involved in arthritis and the T cell receptor genes are being thoroughly studied.

Diabetes

Dr. Leigh Field is a member of the Canadian Network of Centres of Excellence called the Genetic Basis of Human Disease. She is developing genetic markers which researchers can use to look for genes related to diseases, including insulin-dependent diabetes, sometimes called juvenile diabetes.

WORLD FIRST

Dr. Field has developed a new method of tracking the genes for diabetes, which allows her to study families with only one affected family member. Conventional methods require more than one family member and matching families for controls.

Using her new method, she has shown that a gene in the insulin gene region affects susceptibility and that another gene, called G2m(23), is involved. It interacts with two other genes which scientists know make children susceptible to diabetes.

"In the long run, we hope to know what's going on in terms of the aetiology of juvenile diabetes and be able to predict who will get it so we can intervene to prevent it. My goal is to prevent juvenile diabetes," says Dr. Field.

Wilms' Tumors

Eighty North American medical research centres send Dr. Paul Grundy specimens of Wilms' tumors so he can study how genetic changes are related to this childhood kidney cancer. He analyzes the specimens for loss of four chromosomal regions thought to be involved. So far he has evidence that 20 percent of these tumors have lost part of another chromosome, possibly indicating that yet another gene is involved.

When the analysis is complete, he may be able to identify which children are likely to relapse after therapy and therefore should be given more aggressive treatment.

Gout to Kidney Disease

Nucleotides are the building blocks of DNA. Inherited disorders of nucleotide metabolism can lead to many diseases, from severe immune dysfunction to kidney disease to gouty arthritis. Dr. Floyd Snyder has identified mutant genes related to each of these. He is also developing a gene expression system to examine the effects of treatments such as enzyme therapy.

Dr. Snyder is Director of the Biochemical Genetics Lab at the Alberta Children's Hospital. The lab receives pediatric patient samples from physicians throughout Southern Alberta to analyze them for inherited metabolic diseases. For example, failure to thrive might be due to such a condition. His colleague, Dr. Tony Garber, is Director of the Molecular Diagnostic Laboratory at the hospital, offering further genetic screening services as part of the Alberta Hereditary Disease Program.

TB: Comeback of a Killer

DNA technology may come to the rescue to fight a resurgence of an old killer: tuberculosis. In 1992, tuberculosis was called the new epidemic, resurging in the third world because of AIDS, drug abuse, poverty and poor health care. But it is not only a Third World problem: New York City has opened TB hospital wards for the first time in decades. In Alberta, TB increased by 20% from 1989 to 1990, and there have been outbreaks in Northern Alberta Native communities.

One problem is that diagnosis is slow – it can take up to six weeks. Meanwhile, infected people are rapidly spreading the highly infectious disease by sneezing, coughing, even talking.

Dr. Dennis Kunimoto has used DNA fingerprinting technology and the new PCR method of cloning genes to develop a more rapid diagnostic test. It will cut the diagnostic time from six weeks to 48 hours. Earlier diagnosis means faster treatment and fewer infected people, better control of the new epidemic.

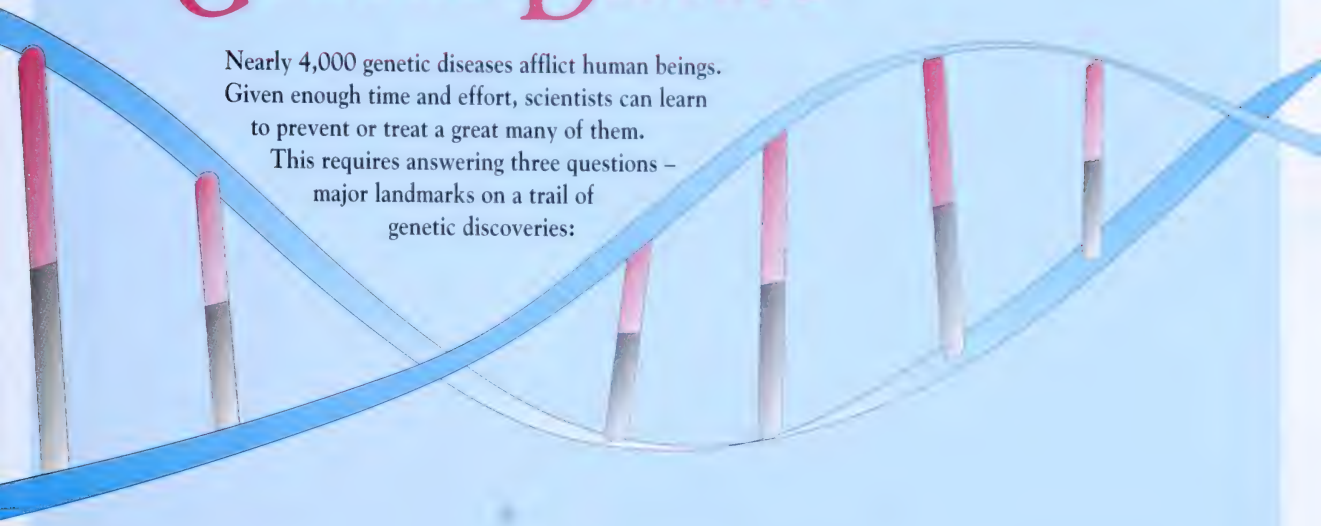
Advancing Technologies

Every DNA researcher – and that includes the majority of basic medical researchers – spends hundreds of hours sorting out the nucleotide sequences in proteins. Dr. Norm Dovichi and Dr. John Elliott have developed a low-cost sequencing instrument that could radically reduce the high costs of this technology and at the same time, extend the possibilities of DNA technology.

They have received AHFMR Technology Commercialization funding to develop the innovation.

How to Conquer a Genetic Disease

Nearly 4,000 genetic diseases afflict human beings. Given enough time and effort, scientists can learn to prevent or treat a great many of them. This requires answering three questions – major landmarks on a trail of genetic discoveries:

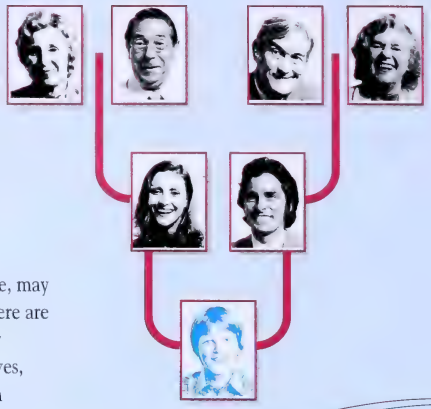


- Which faulty gene causes the disease?
- What protein does this gene normally produce?
- Can the defective protein or gene be fixed or replaced?

Two different strategies may be used. Researchers may find the abnormal protein first (if it can be detected chemically in tissues that are affected by the disease) and then locate the gene that codes for it. When this is impossible, they use reverse genetics: They find the faulty gene first (by zeroing in on the DNA that is inherited with the disease, or by locating a similar gene in a mouse) and then identify the protein that it makes.

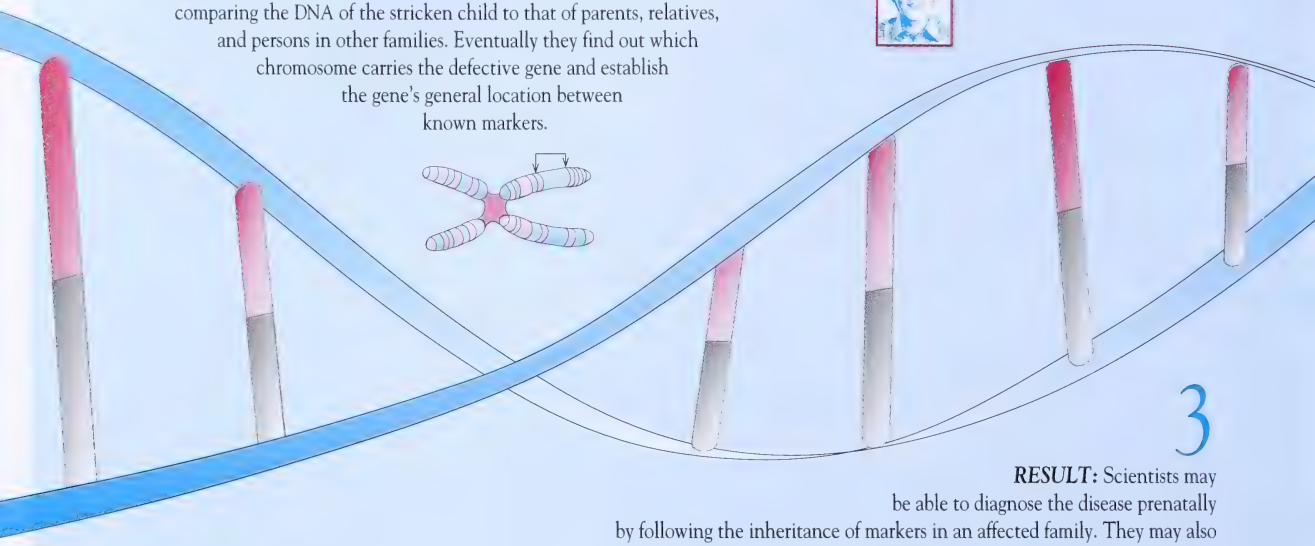
The trail shown here illustrates reverse genetics. This strategy recently led to spectacular progress toward preventing or treating cystic fibrosis, Duchenne muscular dystrophy, neurofibromatosis, and other inherited disorders.

Which gene is at fault?



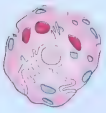
1 A child (bottom box) develops a currently incurable genetic disease. Scientists who wish to find a specific treatment or a means of preventing the disease in other children must trace it to its cause: a faulty gene.

2 Various clues, such as a visibly missing piece of a chromosome, may reveal the gene's rough location on a chromosome. When there are no such clues, researchers look for "markers" of the disease by comparing the DNA of the stricken child to that of parents, relatives, and persons in other families. Eventually they find out which chromosome carries the defective gene and establish the gene's general location between known markers.

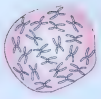


3 ***RESULT:*** Scientists may be able to diagnose the disease prenatally by following the inheritance of markers in an affected family. They may also recognize healthy carriers of the faulty gene. The family shown above has a recessive disease that develops only when a child inherits the defective gene from both parents.

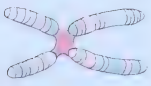
A BRIEF KEY TO BASIC GENETICS



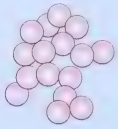
A HUMAN CELL. Each of the 100 trillion cells in the human body (except red blood cells) contains the entire human genome – all the genetic information necessary to build a human being. This information is encoded in 6 billion base pairs, subunits of DNA. (Egg and sperm cells each have half this amount of DNA.)



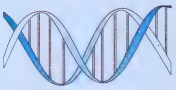
THE CELL NUCLEUS. Inside the cell nucleus, 6 feet of DNA are packaged into 23 pairs of chromosomes (one chromosome in each pair coming from each parent).



A CHROMOSOME. Each of the 46 human chromosomes contains the DNA for thousands of individual genes, the units of heredity.



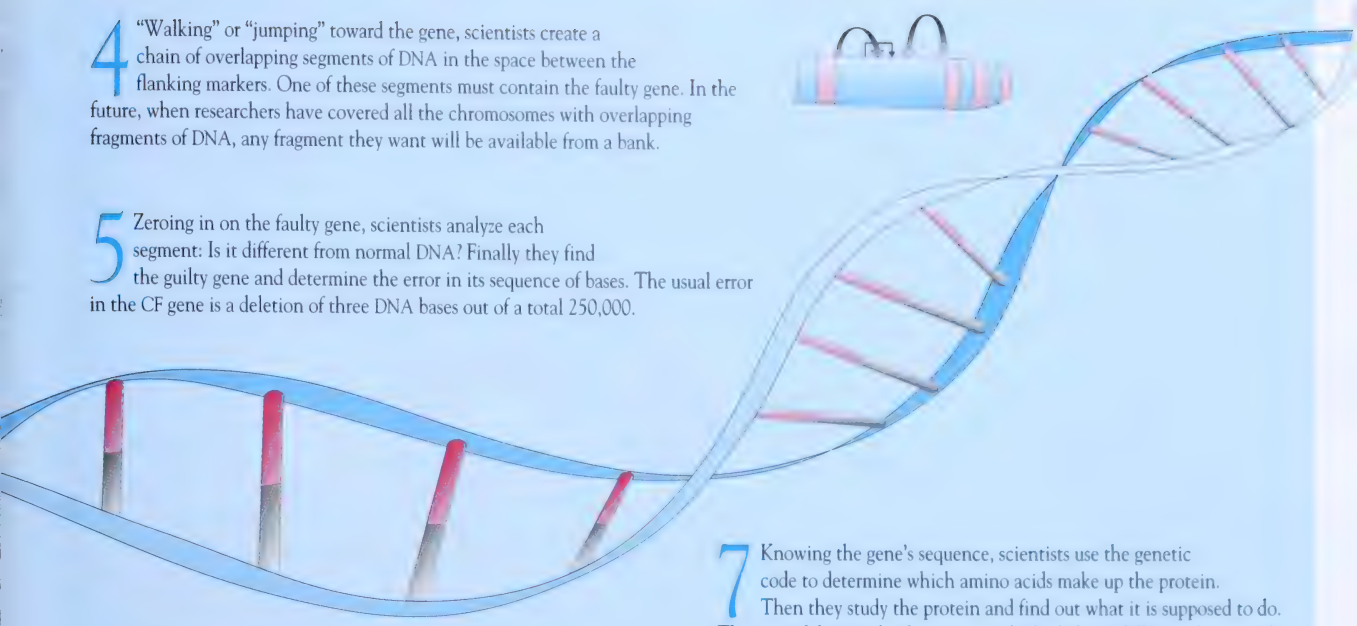
A PROTEIN. Proteins, which are made up of amino acids, are the body's workhorses – essential components of all organs and chemical activities. Their function depends on their shapes, which are determined by the 50,000 to 100,000 genes in the cell nucleus.



A GENE. Each gene is a segment of double-stranded DNA that holds the recipe for making a specific molecule, usually a protein. These recipes are spelled out in varying sequences of the four chemical bases in DNA: adenine (A), thymine (T), guanine (G), and cytosine (C). The bases form interlocking pairs that can fit together in only one way: A pairs with T; G pairs with C.

4 "Walking" or "jumping" toward the gene, scientists create a chain of overlapping segments of DNA in the space between the flanking markers. One of these segments must contain the faulty gene. In the future, when researchers have covered all the chromosomes with overlapping fragments of DNA, any fragment they want will be available from a bank.

5 Zeroing in on the faulty gene, scientists analyze each segment: Is it different from normal DNA? Finally they find the guilty gene and determine the error in its sequence of bases. The usual error in the CF gene is a deletion of three DNA bases out of a total 250,000.



What protein does it make?

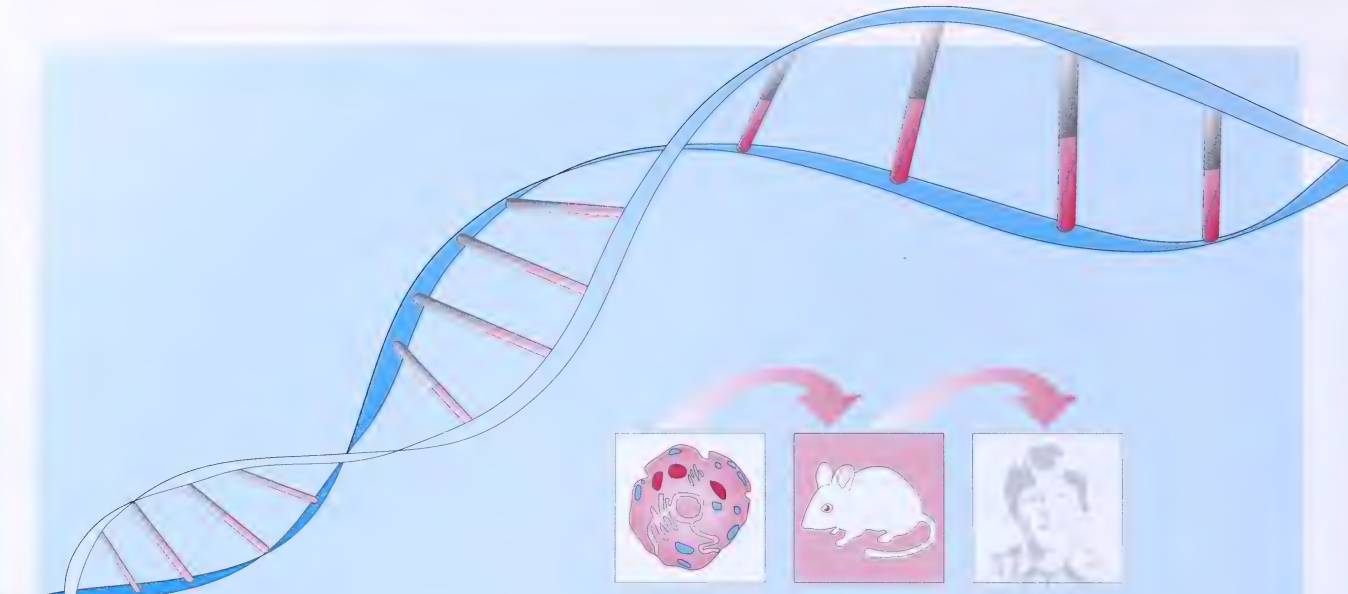
6 ***RESULT:*** Scientists can test for the disease directly in patients (blue box) and prenatally. They can identify healthy carriers of the faulty gene in the general population – not just among members of an affected family. They can study the disease process in cultured cells and in animals, with a view to developing new treatments.

7 Knowing the gene's sequence, scientists use the genetic code to determine which amino acids make up the protein. Then they study the protein and find out what it is supposed to do. The tens of thousands of proteins in the body have different shapes and do different jobs, depending on instructions encoded in the genes.

Can the protein or gene be replaced?

8 Does the sick child's faulty gene produce too little protein, a flawed protein, or no protein at all? Scientists need to understand just how the protein defect causes the disease.

9 ***RESULT:*** As the mechanism of the disease becomes clear, scientists can devise new approaches to treatment involving either the protein or the gene. Understanding a relatively rare inherited disorder may also bring important insights into more common and complex diseases.



10 To make up for the genetic error, scientists may try to replace a missing or ineffective protein with a drug or with the normal protein. Such experiments are usually carried out first in cultured cells in the laboratory, then in animals, and finally in humans.

11 Another option is gene therapy. Some scientists "infect" the defective cells with a virus into which they have inserted normal genes. Others use non-viral methods or even inject DNA directly into cells. Experiments that work in cultured cells are tried in animals and then in humans. For example, a patient's bone-marrow cells may be removed, treated with normal genes, and returned to the patient.

12 ***RESULT:*** Treatments are being developed for some genetic diseases. People will always carry genetic defects, but in the future, prevention and treatment will vastly reduce suffering from genetic diseases.

"How to Conquer a Genetic Disease" on pages 61-64 is reprinted by permission, from *Blazing a Genetic Trail*, a 1991 report edited by Maya Pines and published by the Howard Hughes Medica Institute in Bethesda, Maryland.

Power Failure: CANCER

CANCER IS OVERTAKING HEART DISEASE AS THE MAIN CAUSE OF PREMATURE DEATH.

Biologically, that's not surprising because in a way cancer is a fundamental part of life. The basis of all growth from the womb to life's end is cell division, and cancer is cell division gone crazy. This failure of cell power creates the most complex disease known.

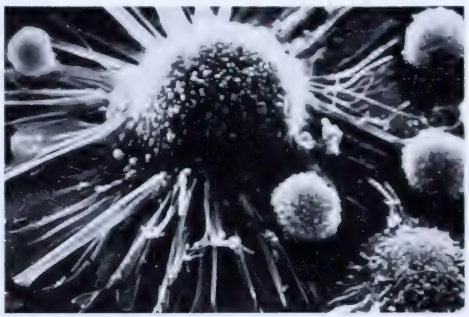
Cancer is not one disease but many, appearing in possibly 200 forms. Nor is cancer a simple cause and effect business like getting the flu because you've been infected with bacteria. A healthy cell becomes cancerous only after many complicated steps.

Fortunately, this is the age of molecular biology, so researchers have new tools to learn how cancer begins and proceeds. This is leading to entirely new approaches to therapies – and none too soon, because we are reaching the limits of traditional treatments (surgery, radiation and chemotherapy), leaving the most common cancers unchecked.

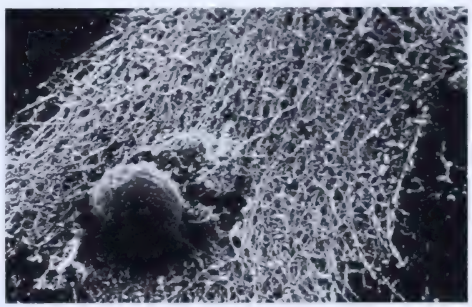
AHFMR supports more than 15 scientists studying cancer by investigating various aspects of the switches that turn cell growth on or off and transform a healthy cell into a malignant one. In the beginning, the switches are the genes, which contain the directions for all cell activity; in later stages, the switches come from many other sources outside the transforming cell.

Heritage groups led by Dr. Randy Johnston at the U of C, and Dr. Grant McFadden and Dr. Malcolm Paterson at the U of A are at the forefront in the hot field of oncogene research.

The following summary of new developments in cancer research shows why we can hope for the future, and where discoveries by AHFMR researchers fit in.



Killer T cells surrounding a growing cancer cell for the attack.



The cancer cell is destroyed, and is nothing but a rubble of filaments.

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What Causes Cancer?

Cancer occurs when genetic and environmental factors interact to increase cell division and cell growth. Tobacco, dietary fat intake, obesity, and ultraviolet light are lifestyle factors that contribute to cancer, and these are controllable. Some cancers are related to hormones. A third group of factors thought to be involved are potentially preventable: viruses, drugs, exposure to X-rays, and constant irritation or trauma. For example, there is strong evidence that the hepatitis B viruses causes liver cancer, so a drug for the virus or widespread immunization would reduce cancer.

Scientists hope to reset the cancer switches which signal cells to grow wildly out of control.

The Destiny of Genes Isn't Final!

Some cancer researchers are fond of the quote, "The seeds of our destruction are in our genes." They are talking about genes which are blueprints for the proteins that regulate the way cells grow and divide. Under normal circumstances, some of these genes are activated only during growth and development before birth, and others during wound healing and normal cell turnover. The products of these genes are called growth factors and they affect cell growth or differentiation (how immature cells decide to specialize).

However, when these genes become inappropriately activated or altered, they become oncogenes. This occurs in many ways. A carcinogen such as ultraviolet light can mutate a piece of DNA. Viruses may be the culprit. Retroviruses pick up small pieces of cell DNA and incorporate them into their own DNA. Larger chromosome changes can occur during the process of cell division if the copying of DNA is faulty. When that happens, the signals are confused so that growth factor activity is uncontrolled.

So far, 50 to 100 oncogenes have been identified. Recently another discovery further complicated the cancer story, and fortunately so. There are also anti-oncogenes, sometimes called tumor suppressor genes, which have the blueprint for proteins that stop cell division. Apparently, cancer won't occur unless oncogenes are activated and tumor suppressor genes are faulty. The discovery of these new checkpoint genes has opened up another avenue for cancer therapy.

Cell Talk

Scientists are now unravelling the multiplicity of signals related to growth factor activity and to the immune cells designed to destroy tumor cells. *(See page 41.)* Every time they discover a critical point on the path of signals, there is potential for stopping the process.

For example, some researchers are unravelling the signals that lead to metastasis. In many cases, it is not the initial tumor, but the spreading cancer that kills. Since new tissue is always being created and destroyed, where does the process go wrong so that cancer cells cross normal barriers?

Other researchers look at cell adhesion molecules (CAMs), the molecules on cell surfaces that hold cells together so they can "talk" and receive the messages to divide or stop dividing.

In all these areas, the goal is to reset the switches, and scientists are finding the tools to do it.

WHAT'S NEW IN CANCER DIAGNOSIS AND TREATMENT?

Gene Probes for Diagnosis: Researchers have developed molecular probes to detect excess copies of oncogenes in some cancers. By monitoring the oncogenes they pick up clues as to which cancers are most aggressive and should be treated accordingly, and they can see how the cancer responds to treatment. Extra copies of a gene called Her-2/Neu or erbB-2 seem to show which women with stage one breast cancer will go on to more severe stages. Other gene probes are being used to diagnose some lymphomas and a type of leukemia.

Watching Cancer Begin: Researchers are finding ways to "watch cancer begin" by detecting an excess of certain signalling molecules, which heralds danger long before tumors actually appear. This could lead to new diagnostic tests.

Magic Bullets: Monoclonal antibodies (Mabs) are antibodies genetically engineered to hit very specific targets (receptors) on tumor cells. When fluorescent markers are attached to the Mabs, the cancer cells are lit up for accurate diagnosis and monitoring of treatment. When a drug is attached to a Mab it is delivered directly to the cancer cell, a process that many researchers are working to refine.

Laser Light: Some cancers respond to phototherapy, which destroys cells by a different method than chemotherapy or radiation. Light-sensitive drugs head straight for tumor cells and when laser light is shone on them, a reaction occurs that results in destruction of the cancer cell membranes. So far the therapy works only for surface tumors and there are some complications.

Colony-Stimulating Factors: These growth factors encourage the reproduction of white blood cells, enabling a cancer patient to tolerate high doses of chemotherapy. Applying other growth factors may increase the effectiveness of chemotherapy at certain stages of cell proliferation.

Interferons and Interleukins: These substances are normally produced by immune cells to fight tumors and other disease. Interferon has been used to successfully treat hairy-cell leukemia and is being experimentally used for other cancers. Since interferon alfa-2 was found effective, researchers began experimenting with other growth factors such as interleukin-2. They apparently work by inhibiting oncogene expression, enhancing expression of other genes, and increasing the effectiveness of other immune cells.

Boosting T Cells: Dr. Steven Rosenberg of the National Institutes of Health in Maryland pioneered an interleukin therapy where, instead of giving it directly to patients, their own T cells were harvested and treated with interleukin then returned to the body. He has had promising results, but there are serious side effects.

Gene Therapy: Dr. Rosenberg has started controversial gene therapy. He takes tumor-infiltrating cells from cancer patients and incorporates the gene for tumor necrosis factor, a protein that interferes with a tumor's blood supply. Then the cells are injected back into the patients' tumors. But so far there is no proof of safety or effectiveness.

Other American researchers have inserted into brain tumor cells a gene for a substance that will make the cell vulnerable to a drug. Still others hope to reactivate tumor suppressor cells they believe have failed and led to melanoma.

New Chemotherapy: Researchers use recombinant DNA technology to make drugs that combine toxic material from a bacteria or plant with growth factor or antibody protein that will head straight to proteins or antigens on tumor cells. These combined drugs kill tumor cells by a different means than conventional chemotherapy. This work is in the very early stages of experimentation.

❖ DR. MALCOLM PATERSON has helped develop the Her-2\Neu gene probe for detecting which women with stage one cancer will have a relapse.

❖ DR. KOWICHI JIMBOW has developed a test for diagnosing melanoma earlier and he has discovered a promising drug which might eliminate the disease.

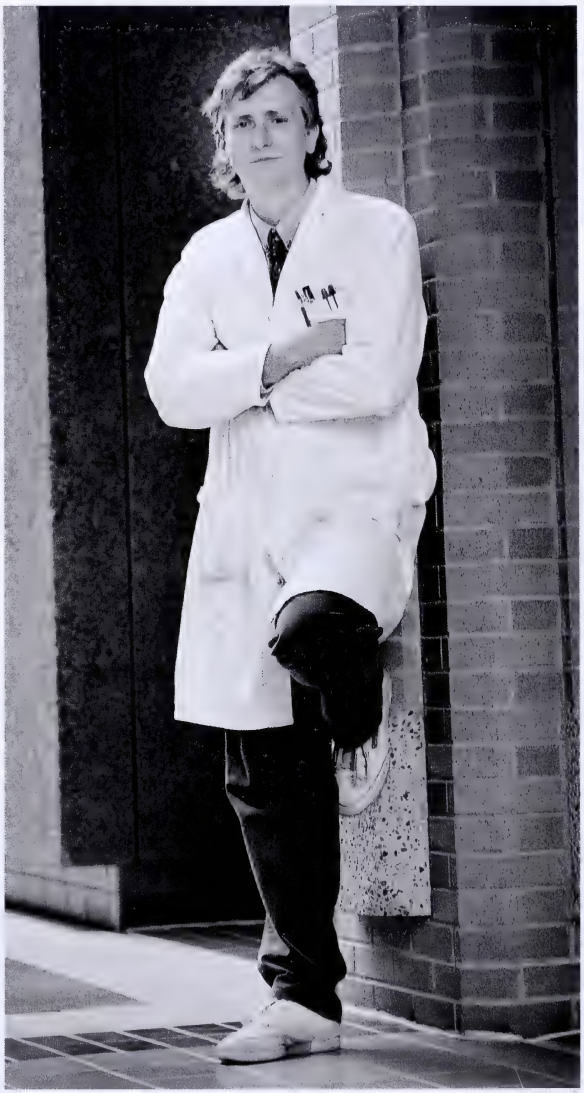
❖ DR. DYLAN EDWARDS has shown that the most metastatic non-Hodgkin's lymphoma cancers show a shortage of a particular protein, that normally prevents enzymes from breaking down too much connecting material between cells. If these proteins operate properly, tumor cells may not be able to go through the connecting material to invade other tissues.

This protein shortage appears before the tumor spreads, so it could help doctors detect who should be treated aggressively before metastasis occurs. It could also lead to a new drug designed to stop the enzymes from inappropriately breaking down intercellular material.

❖ DR. RONALD MOORE has a lead on an improved light-sensitive drug for photodynamic therapy for prostate, bladder and other cancers.

❖ DR. CHRISTOPHER BROWN has developed a method for studying how a blood cell growth factor binds to a molecule on the surface of the blood cells and controls growth. He has also found a free-floating receptor molecule for this growth factor.

This new form may be clinically useful because the growth factors are used to promote blood cell growth in cancer patients who have had chemotherapy or bone marrow transplants.



Dr. Dylan Edwards

❖ Dr. Saul Zackson has established a facility for creating transgenic mice. By introducing foreign genes into mice, they become models to study how oncogenes affect cell growth and differentiation to produce cancer.

❖ Dr. Grant McFadden has discovered a new way tumor-causing viruses subvert the immune system designed to fight such infections. He also has clues as to how the immune cells recognize and reject cells infected with viruses or non-viral cancer cells.

❖ Dr. Dallan Young has identified a gene called CAP which is necessary for proper function of the RAS gene. Mutants of RAS are associated with a quarter of all cancers.

❖ Dr. Karl Riabowol's study of the FOS oncogene has led to a possible explanation of why cells lose the ability to divide and to regulate cell growth as we age.

❖ Dr. Bruce Stevenson has new insights into the function of the CAM molecules so necessary for proper signalling between cells.

❖ Dr. Susan Rosenberg has discovered a protein that is turned off when mutations occur in genes of non-dividing bacterial cells. The discovery could be an important clue to how mutation leads to human cancers.

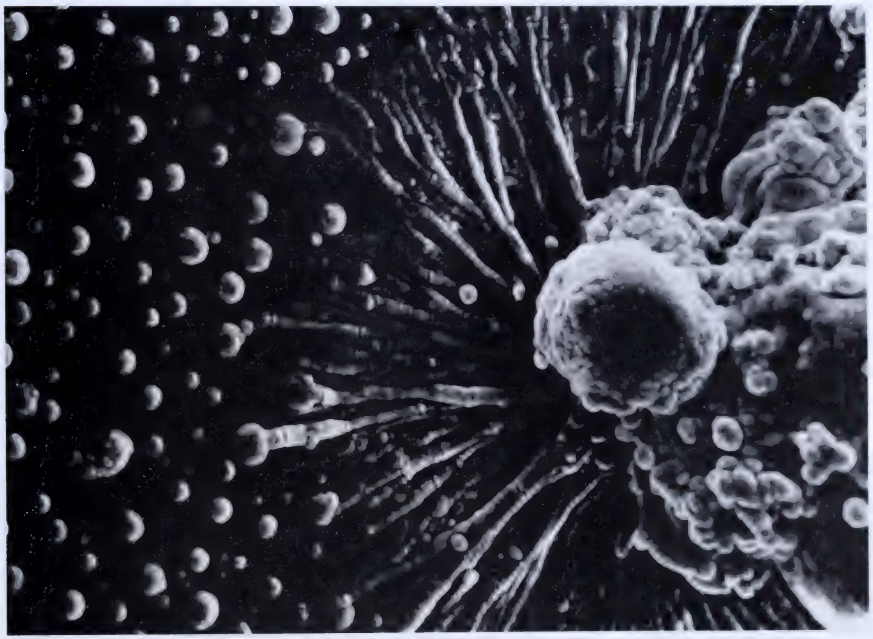


Photo courtesy Boehringer Ingelheim Canada

THE POWER OF THE PILL

HOW DOES A DRUG KNOW WHERE TO GO IN THE BODY? Well, often it doesn't and we get side effects, some a nuisance, and some potentially lethal.

Molecular biology techniques are making it possible to design drugs targeted to specific molecules in the body and not others.

Monoclonal antibodies (Mabs) are one solution. Mabs are proteins engineered to hook on to another specific protein (called an antigen) on a molecule in the body. A drug can be attached to a carrier Mab headed for the right place.

Then there's the idea of designing the drug correctly in the first place. Researchers call this "rational" drug design as opposed to the old hit-and-miss method of screening thousands of substances in culture dishes and animals to see which compounds have some effect (though nobody would know quite how or why).To rationally design drugs you have to know precisely what's wrong at the molecular level so you can fix it.

The best-designed lab-tested drug must go through patient tests, while safeguarding patient safety at all stages. To get a new drug on the market, the process from lab to clinic takes about 10 years and millions of dollars.

That's why, increasingly, pharmaceutical companies look to university expertise for new leads or assistance. In Canada, they very often partner with AHFMR scientists.

Because of their excellence, AHFMR researchers participate in national and international cooperative tests of drug therapies for: arthritis, colitis, epilepsy, Alzheimer's disease, asthma, cystic fibrosis, cardiac disease, cancer, AIDS, and many other diseases.

Other AHFMR researchers are solving serious problems created by side effects of drugs we must use until something better is found.

A Safety Net for Heart Failure Patients

Some Canadians may want to thank bacteria in a culture dish for saving their lives, in a round-about fashion.

The *B. subtilis* is a medicine factory, making an antibody which can detoxify congestive heart failure patients who could die from the very drug given to save them.

Digoxin will rescue a failing heart, but if the dose is not precisely appropriate, patients have a life-threatening reaction. Then their blood is purified in a complex, expensive process but the therapy doesn't always work.

Dr. Sui Lam Wong has developed a Mab which will take up the extra digoxin, thereby eliminating the lethal toxicity quickly and simply. He did it with his innovative biotechnology system which gets *B. subtilis* bacteria to copy and express genetically engineered medical proteins.

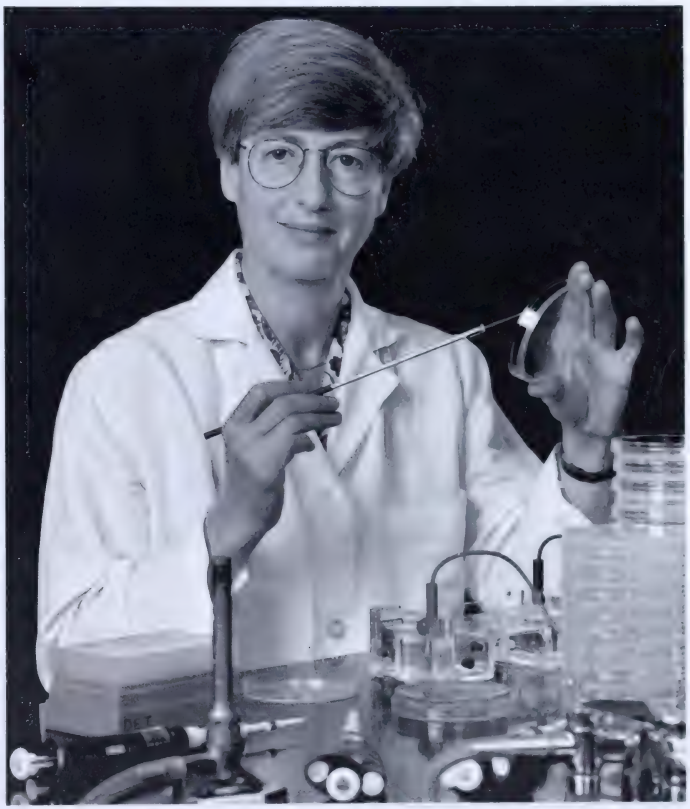
Outsmarting Bugs

Many of us owe our lives to antibiotics which have largely relegated influenza epidemics and other plagues to dark history. Yet evolution never stops and bacteria, one of the most ancient life forms on the planet, have learned a few survival tricks over the millennia. They mutate and therefore are increasingly resistant to antibiotics.

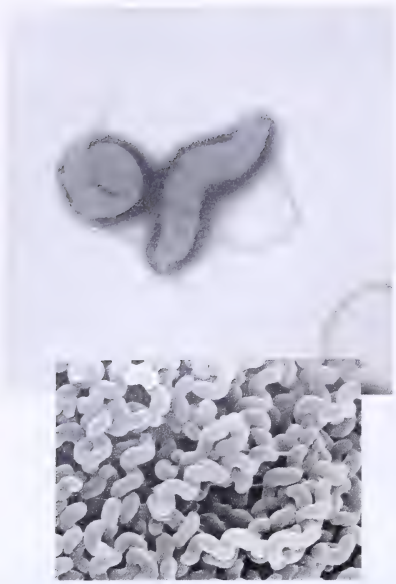
Once again, modern biologists tackle the problem by understanding how this resistance occurs at the genetic and molecular levels.

Dr. Diane Taylor has discovered how small circles of bacterial DNA, called plasmids, carry antibiotic resistance. This is the first step in counteracting it. Along the way, she has developed gene probes for diagnosing blood poisoning and other infections more quickly. One of the bacteria she studies is *C. jejuni* *(See page 72.)*

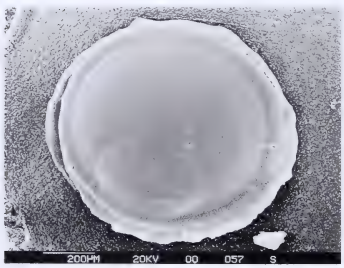
When you inhale the earthy perfume of garden soil, you're smelling the bacterium called *Streptomyces* which happily produces antibiotics but unfortunately, not in the amounts needed for cost-effective commercial production. Dr. Brenda Leskiw exploits natural mutations of *Streptomyces* to understand nature's antibiotic production and find ways to speed it up.



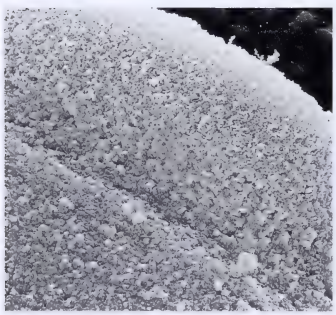
Dr. Diane Taylor



These electron microscope photos show spiral and coccoid forms of the bacterium C. *jejuni*, which causes food poisoning (gastroenteritis).



A colony of C. jejuni.



A portion of a colony.

The Kool-Aid Kids

Complex problem? Try a simple, brainy solution. Doesn't always work, but it did for the Kool-Aid kids, Drs. John Meddings, John Wallace and Lloyd Sutherland, gastrointestinal researchers at the University of Calgary. On the strength of their combined expertise, Searle Canada chose them over everyone else in the country to solve a problem with the side effects of arthritis drugs called NSAIDs.

Widely prescribed to reduce inflammation, NSAIDs sometimes cause silent, potentially-fatal bleeding ulcers. The task was to design an effective way to detect the ulcers earlier. The Calgary team came up with the simple Kool-Aid test. Drink it and measure the sucrose (table sugar) in urine because if it's there, it's leaked through holes in the stomach lining instead of being absorbed as it normally would be.

The Kool-Aid test is in trials across Calgary. If its promise holds true, fewer patients will have an uncomfortable and very expensive endoscopy (tube down the throat) to check for ulcers. Fewer still will end up in the emergency ward with bleeding ulcers they had no idea were there.

Pressure for High Blood Pressure Drugs

Researchers working in the field of high blood pressure drugs are in danger of getting the disease themselves, so intense is the competition – and for good reason. Because the majority of senior citizens have high blood pressure, the financial stakes are high. At the same time, the drugs are far from perfect and have many side effects.

Two AHFMR projects illustrate how basic research could lead to more potent, and safer drugs by finding out just what causes hypertension. Presently, there is no known cause for the majority of cases.

Dr. Michael Walsh has discovered how two proteins control contraction of the smooth muscles lining blood vessels. His research earned him the prestigious 1990 Steacie Prize given annually to an outstanding young Canadian scientist.

Biochemist Dr. Christina Benishin found one molecule among a million in plasma, and now she's trying to solve its structure. The molecule is called Parathyroid Hypertensive Factor, identified by Dr. Richard Lewanczuk. The U of A team, led by Dr. Peter Pang, thinks PHF could account for high blood pressure in about a third of the people who have it for no apparent reason.

KEEPERS OF THE PROMISE:

The Crystal Lady

NATALIE STRYNADKA IS A CRYSTAL LADY – not the fortune-telling kind but the scientific kind. She doesn't predict the future: she helps shape it. She uses crystals to see into the inner universe, the molecules in our bodies.

Dr. Strynadka is one of the world's rising X-ray crystallographers. Using unprecedented computer technology at the University of Alberta, she can study molecules so small that about two million of them placed side by side equal a finger's width. First, beautiful crystals of molecules are created (a scientific challenge in itself). X-rays shone through the crystals produce diffraction patterns according to the atomic structures. These patterns are then translated into another thing of beauty, 3-D computer images of the molecules.

By studying such images, scientists can design other molecules to attach to the molecules pictured. In this way, new drugs and drugs with fewer side effects can be precisely designed.

Using X-ray crystallography, Dr. Strynadka has done something other people in the world have been unable to do – she has analyzed how bacteria resist antibiotics. They release an enzyme called beta-lactamase that attaches itself to the antibiotic molecule and prevents it from breaking down the bacterial cell walls.

Working with Dr. Susan Jensen, she has solved the structure of a protein that inhibits beta-lactamase. This means that instead of changing antibiotics, scientists could design a drug that blocks the enzyme so that existing antibiotics could do their job.

Dr. Strynadka was recognized by the Natural Sciences and Engineering Research Council of Canada as one of Canada's best PhD graduates. Her thesis covered several areas, including how antibodies bind to fight a herpes virus (useful for developing a vaccine) and how 40 proteins bind to calcium ions. Some of these proteins are targets for drugs used to treat heart disease and schizophrenia.

Why a Scientist?

Natalie grew up in Edmonton with parents who enjoyed the outdoors and spent a lot of time at the family summer cottage. Though she almost became a musician, X-ray crystallography won out because, she explains:

"I always wondered why things were the way they were, and I'm very visually oriented. That's what attracted me to crystallography. You can see how atoms are arranged: It's a very artistic kind of science. I was attracted to biochemistry because it is the fundamental level of understanding things. You have the basic science of chemistry, but you can apply it to the real world, to biology and nature, and that seemed the right combination. Then in X-ray crystallography you have the visual stimulation."

With so many accomplishments in a hotly competitive field, is Natalie Strynadka a nerd locked away in dark rooms, hunched over the computer terminal? Never.

"You go through periods where you work very hard and the work's very close and exciting. It can be very intense, but you need other stimulation....There are times when I feel the pressure of competition, but generally I try to keep a fairly balanced life," she says. She hikes, canoes, skis, plays the piano, and volunteers for community activities.

"If I'm going to do this for the rest of my life, I can't get stressed out every time I have to write a paper. I'll just end up hating it. I remember that I'm here because it's interesting and I love it."

Did she ever have doubts? "I never worried about not being able to find the answers I set out to find, but the doubts come in when you don't know where you will get a job and you know you have to continually justify your funding until you retire."

"I'd like to say it was quite a boost to have the AHFMR studentship. It made me feel I had someone backing me up. The support meant the ability to travel and meet other scientists for a very rewarding exchange of ideas and problems. I felt the responsibility too, because this is public funding.

"It's been fun and I feel very lucky. Sometimes when I'm in front of the computer moving molecules around, I can't believe I'm getting paid to do what I love."

Dr. Strynadka now holds a J. Gordon Kaplan Memorial Post-Doctoral Fellowship to work with Dr. Michael James, who also supervised her doctoral studies.

INNER CITY HEALTH

Lisa Gaede with colleague Callum Grainger

THE BOYLE-MCCAULEY HEALTH CENTRE cares for inner-city people with problems – the poor, the immigrants, the unemployed, and generally the forgotten people. Half of the clients are Native.

In the summer of 1992, U of A medical student Lisa Gaede was funded by AHFMR to help the Centre survey Native clients. Were they receiving the care they needed?

Lisa's survey indicated the Centre is doing a good job, but the health problems are complex and closely related to three big problems: alcohol abuse, poor housing and emotional stress.

"I learned health is much broader than I'd thought," says Ms. Gaede of the experience. "Coming from a different background, all my needs are satisfied and health is separate from that. The health problems of the people here are intertwined with their living conditions, and for many people, health concerns are less important than basics like food or rent."

"I also learned how cultural values and beliefs relate to health care." She is convinced the experience was invaluable education for her future work as a physician.

In 1991, AHFMR funded Lisa Gaede to work as a story researcher on the Edmonton CBC radio morning show. Lisa was part of the AHFMR Media Fellowship Program designed to increase the quality and quantity of science coverage in the media.

2000

young people

have been

supported

under AHFMR

training programs.

DRUG TRIAL FOR CHRONIC FATIGUE SYNDROME

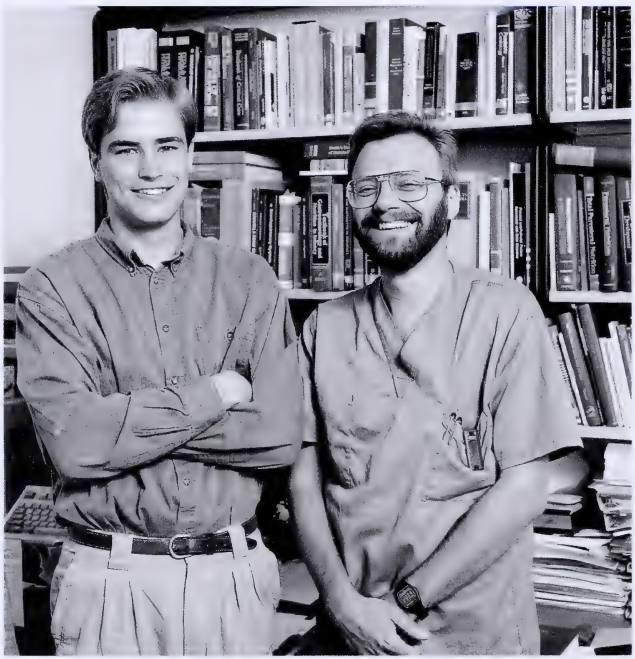
The summer of 1992, U of A medical student Niels Koehncke found himself telephoning patients who were grateful to have someone listen to their story. The patients had been diagnosed with the controversial disease, chronic fatigue syndrome, and many of them had been told it was all in their head.

Mr. Koehncke was gathering data from the patients as part of a drug trial, mounted by Dr. Johny Van Aerde and six colleagues at the U of A who are also identifying measurable physiological symptoms of the disease.

The study opened Mr. Koehncke's eyes to the complexities of executing clinical trials and to the real world of medicine.

"Patients told me, 'Thanks so much for listening.' It was rewarding in that sense. In class they drill into us that the best thing you can do is listen, but it never sinks in, till you've done it. I would hang up the phone and realize I'd hardly said a thing, but the patients felt better for some reason."

For two summers prior, AHFMR funded Niels Koehncke to do summer research in two basic biology labs.



Dr. Johny Van Aerde (*right*) with medical student Niels Koehncke

Summer Students

In the summer of 1992, two other medical students opened up new research territory. Ieleen Taylor conducted a pilot study on ambulance use and abuse in Edmonton. Carol Fong worked on a study proposal for assessing how pulp mill development in Northern Alberta affects health.

Every summer AHFMR funds about 140 summer undergraduate students to work under supervisors. About 150 full- or part-time Masters and Doctoral students are supported throughout the year. Since 1980, about 2000 young people have been supported under training programs, providing unprecedented opportunities for research training.

Ms. Jill Kleebaum

For six weeks in 1992, Sherwood Park grade 11 student, Jill Kleebaum, got a taste of life in the lab. She looked for a chemical test to identify the presence of an enzyme on a protein molecule found on the surface of all white blood cells. Ms. Kleebaum was assigned the task by her supervisor, Dr. Hanne Ostergaard, who is investigating how Tcells in the immune system recognize danger and mount an appropriate immune response.

"I've learned a lot just by listening to everyone in the lab, and I've learned that it can take a long time to do just a tiny thing," says Jill Kleebaum. Dr. Ostergaard laughs because she had to learn the same thing: patience.

Jill Kleebaum's summer research was part of the 1992 summer research program organized by Women in Scholarship, Engineering, Science and Technology at the U of A to promote science careers for females.

School Science Fairs

Through the National Youth Science Fair Program, AHFMR promotes science education for Alberta school students. There is an AHFMR Award of Excellence in the Life Sciences for each of the eight regional science fairs in the province. The awards pay students' airfare to the National Fair and offer them an opportunity to visit an Alberta medical research lab.

POWER OF AN IDEA:

TECHNOLOGY COMMERCIALIZATION

THE SCENE IS CHICAGO AT THE JULY 1992 INTERNATIONAL SYMPOSIUM ON PROSTHETICS AND ORTHOTICS. Edmonton engineer Kelly James has arrived with an artificial leg under his arm, a prosthesis like no other in the world. This electronically-controlled, above-the-knee prosthesis adjusts to the terrain, makes climbing stairs easier and the gait more natural.

Industry quickly recognized quality innovation and began to court Mr. James, the unknown "little guy" who has built his small company, Biomech Designs Ltd., on the power of a bright idea.

Six months later Mr. James signed an agreement with Otto Bock Orthopedic Industries Ltd. of Germany to further develop his innovation for the world market. He then hired Alberta companies to do the electronic assembly, frame-building and additional computer programming for the first production run of the prototype.

"AHFMR funding allowed me to take my research idea into the real world and produce a professional prototype to show investors," says Mr.James. "I'm excited about getting this in the world market to help amputees in their daily lives."

From Lab to Marketplace

Kelly James is one of the entrepreneurs backed by the AHFMR Technology Commercialization Program, which funds the commercialization of medically-related innovations so new technology can be translated into improved health care.

The program promotes research/industry collaboration, and fills the funding gap when a commercially promising project does not fit the mandate of traditional medical research funding agencies and is not developed enough to attract outside investors.

Since its inception, the program has supported 65 innovations under three categories of phased funding: Phase 1, up to $25,000 to assess technical aspects and explore market potential; Phase 2, up to $75,000 for developing prototypes, marketing plans and intellectual property protection; and Phase 3, up to $500,000 to support final product development, marketing strategies and clinical trials. Phases 2 and 3 have pay-back agreements if the project is successful.

Phase 3 is funded by Medical Innovation Program money from Government of Alberta federally transferred funds.

Innovative medical devices, drugs, health care delivery systems, therapies, and medical research instruments have all received funding.

Some projects have attracted additional funding, some have been patented and licensed and some have generated new companies. Most are still in the lengthy technology commercialization process.

***Opposite page*: Mr. Kelly James**

THE MOVERS AND THE MAKERS

The program brings together the makers – bright idea people in university labs, hospital wards, engineering firms, computer companies, offices – and the movers – entrepreneurs that drive the business end of innovation.

New Vaccine: Dr. Robert Hodges, a protein chemist at the University of Alberta, is President of Synthetic Peptides Inc. (SPI), an Edmonton company boldly challenging multinationals in the field. It does so on the strength of expertise in making synthetic peptides, pieces of proteins used as drugs, vaccines and diagnostics.

The company's big project is the development of a *pseudomonas* vaccine to prevent the dangerous *pseudomonas* infection common in hospital patients, people with cystic fibrosis, and others with weakened immune systems.

"A Phase 2 Technology Commercialization grant helped get our company off the ground. Now our Phase 3 grant is supporting further development of our *pseudomonas* vaccine and the thorough review process we went through to get the Phase 3 is giving us credibility with our investors," says Dr. Hodges.

Research Tools: President Cliff Anger and engineer Stephen Babey of Itres Research Ltd., Calgary, realized that their imaging technology used in forestry and agriculture could be adapted for medical research and environmental monitoring. With TC funding, they have teamed up with U of A plant geneticist Dr. Aladar Szalay to develop a highly specialized research camera. The camera focuses on a potential $500-million market.

The Edmonton firm, Professional Diagnostic Inc. (PDI), is marketing another innovative research tool around the world. It's a blender for homogenizing tissue, developed by Calgary biochemist Dr. Frans van der Hoorn. Mr. Garth Likes, President of PDI, has discovered the market is bigger than was thought – virtually every molecular biology lab in the world.

An Electronic Companion for the Elderly: Dr. Tom Nelson, a U of A psychologist, and engineer Brad Belke, President of Integrated Communications Technologies Ltd., are developing an electronic companion for the elderly. It's a much more sophisticated version of the emergency response systems currently on the market. The innovation has voice interaction so the "companion" can ask, "Did you take your medicine? Who do you want me to dial for you on the phone?"

Catheter for Clearing Arteries: When engineer Alex Palynchuk thought he might need to have balloon angioplasty to clear his arteries, a procedure with some risks, he decided to invent a better option. Mr. Palynchuk, President of Western Instruments Inc., of St. Albert, has devised an ultrasound catheter for unblocking arteries. The product is being tested by cardiologist Dr. Alexandra Lucas.

Preventing Suicide: A psychiatrist, a psychologist and two social workers have parlayed a cottage industry into Livingworks Education Inc., a company which is marketing a suicide prevention program world-wide. The program has helped 50,000 caregivers in Alberta, Canada, and California learn to recognize warning signs of impending suicide attempts and develop counselling skills. TC funding is supporting expansion into international markets.

Coldbuster Bar: Dr. Larry Wang's Coldbuster Bar got a little help from AHFMR. In 1984, when Dr. Wang was just beginning development on the bar, AHFMR gave him a Professor-in-Residence award to free him from university teaching responsibilities for a year.

AHFMR funded research spins off new business opportunities for Albertans.

THE POWER OF EXCELLENCE

EVERYBODY KNOWS...

Money is Power – and Power is Money

As of 1992, AHFMR researchers attract two research dollars from other funding sources for every dollar AHFMR invests in them.

❖

This is a measure of their excellence and their high ranking nationally and internationally in very competitive fields.

❖

Every dollar AHFMR attracts to the province builds Alberta's growing science- and technology-based economy.

Drug Company Invests Up to $15 Million

Glaxo Canada earmarked up to $15 million for the Glaxo Heritage Institute for Virology research at the University of Alberta. The company has already provided an initial $800,000 for construction and $550,000 a year for operating expenses.

Dr. Jacques Lapointe, President of Glaxo Canada, made it clear that the company is investing in excellence, demonstrated by the outstanding leadership and achievements of Dr. Lorne Tyrrell, who heads the Centre, and by the Alberta research community largely in place because of AHFMR support.

AHFMR has given the virology team $1.8 million, including a Technology Commercialization grant for initial work on hepatitis B drugs. The grant allowed Dr. Tyrrell to give Glaxo preliminary evidence for the compound's effectiveness.

The University Hospitals Foundation and the former provincial Department of Technology, Research and Telecommunications each contributed $200,000 to the Institute.

A Big Bite of the Centres for Excellence

AHFMR researchers are well-represented in the national Network of Centres of Excellence, particularly in the Neural Regeneration and Functional Recovery Network and the Canadian Bacterial Diseases Network. A total of 15 AHFMR scientists participate and other members of the networks have been supported by AHFMR grants for students and fellows, equipment, and lab facilities.

MRC Honors

Dr. Jerry Wang heads the new MRC Group in Signal Transduction at the University of Calgary. He and three other AHFMR researchers were granted $3.1 million from the Medical Research Council of Canada.

JDF Centre of Excellence

Dr. Alex Rabinovitch and Dr. Ray Rajotte head one of the six North American Centres of Excellence funded by the Juvenile Diabetes Foundation International. The U of A diabetes group was awarded $3.55 million under the program. McGill University is the only other Canadian recipient of the award.

The islet transplantation team receives additional support from the University of Alberta Hospitals, the McLaughlin Foundation for Diabetes Research, the Edmonton Civic Employees Charitable Assistance Fund, the Medical Research Council of Canada, the Muttart Diabetes and Research Training Centre, the Alberta Foundation for Diabetes Research, and the Canadian Diabetes Association.

SIDS Researcher Well Funded

Dr. James Fewell exemplifies AHFMR researchers who attract impressive outside dollars, a million from 1987 to 1992. Last year he and three Australian researchers were given $800,000 from the National SIDS Council of Australia. Dr. Fewell also receives major support from the prestigious National Institutes of Health and holds an MRC Scientist Award with salary support. The Heart and Stroke Foundation of Canada and the Alberta Lung Association have also given him operating grants.

More Industry Funding

Dr. Tony Schryvers is receiving $650,000 from Institut Mérieux for his meningitis vaccine studies. MRC contributed $50,000 as part of the Industry/MRC package. Dr. Schryvers has attracted $900,000 in total funds, including support from the Centre of Excellence for Infectious Diseases and the pharmaceutical company, Eli Lilly.

Howard Hughes Institute Awards

AHFMR researchers received two of the first 11 international awards from the esteemed Howard Hughes Medical Institute in Maryland. Dr. James McGhee and Dr. Randy Read each received grants of more than half a million dollars. The third Alberta winner, Dr. Tim Mossman, is Chair of the Department of Immunology at the U of A and recipient of an AHFMR establishment grant.

Since AHFMR was established, MRC funding to Alberta has increased from $5 million to $27 million, a proportionately greater increase than any other province.

Power of Partners

THIS IS THE AGE OF PARTNERS, AND CERTAINLY NO SINGLE AGENCY can meet the challenges of providing better health. In funding individuals and programs, AHFMR partners with universities, hospitals, government, voluntary agencies, community donors, industry and other research organizations.

AHFMR supports research positions – paying scientists' salaries, setting them up in a lab that may cost from $100,000 to half a million, funding students and fellows in the lab, and assisting universities with overhead costs. Then every researcher is expected to get operating funds from other organizations in peer-reviewed competitions.

The system ensures that researchers are competitive in their fields and that research funding efforts are not duplicated. The following is only a sampling of these partnerships.

Dr. Nellie Radomsky

DOCS ON THE FRONT LINE

Dr. Nellie Radomsky of the Parsons Clinic in Red Deer became concerned about a group of women patients with chronic illness and pain. Why didn't they respond to care as other patients did? Why did they have such an unusual amount of illness? Nothing in Dr. Radomsky's traditional medical education provided the answer.

Therefore, she set about doing a research project in the context of family systems, and discovered that the chronic illness and pain were related to how patients were raised.

To execute the study, Dr. Radomsky received help from Dr. Wayne Elford, Director of the new Primary Care Research Unit (PCRU) in Alberta. The PCRU was developed in 1992 by family practice researchers, Dr. Elford at the U of C and Dr. Neil Bell at the U of A. The organization provides research expertise to GPs in the community. It is associated with the Alberta Family Practice Research Network funded jointly by the PCRU and the Alberta Chapter of the College of Family Physicians and Surgeons.

Family doctors in Alberta now have a way to chase down answers to the nagging questions arising on the front line of medicine, the doctor's office. Most often, they are questions relating to general health, questions not covered in disease-oriented specialty medicine and research.

Three Funding Partners

The PCRU is possible because AHFMR, industry and a private foundation partnered in the venture. The Max Bell Foundation of Toronto, Janssen Pharmaceutica, and AHFMR each contributed a third of the funds to establish the PCRU.

SO WHAT'S THE BEST TREATMENT?

Is surgery more effective than drug therapy? Which treatments reduce hospital stays? Do new drugs for high blood pressure work?

Finding the answers to these questions requires complicated, extraordinarily expensive clinical trials involving hundreds or thousands of patients in many medical centres.

AHFMR has funded two crucially needed clinical trial centres, one at the Centre for the Advancement of Health at the Foothills Hospital, and one at the U of A, called the Health Care Outcomes Research Centre. Through this special initiative, AHFMR is making possible research activity that universities and hospitals could not support on their own.

CANCER RESEARCH PARTNERSHIPS

In 1989, Dr. Grant McFadden was given one of the first three Terry Fox Development Awards from the National Cancer Institute of Canada (NCIC) to recruit new investigators to the University of Alberta, four of them AHFMR researchers. The Terry Fox team is cooperatively funded: with $675,000 from the Terry Fox Fund and $465,000 from NCIC, both over three years, and $1 million from AHFMR over five years.

Support for Dr. Malcolm Paterson, an AHFMR scientist at the U of A and Cross Cancer Institute, is another example of joint funding for cancer research. Like many AHFMR researchers, he receives substantial funding from the Alberta Cancer Board, the National Cancer Institute of Canada and the Medical Research Council of Canada. Other funds come from a small U.S. research foundation, from the IRAP program of the National Research Council of Canada and from Vencap Equities Alberta Ltd., the latter for commercialization of a diagnostic test for breast cancer.

Between 1990 and 1993, Dr. Paterson brought in more than $900,000.

CREATING AN ASTHMA CENTRE

Alberta now boasts an asthma centre, led by AHFMR researcher Dr. Dean Befus, to address this growing and potentially fatal problem. The Centre relies on the expertise of AHFMR researchers in both Calgary and Edmonton. Funding to establish the Centre came from the Alberta Lung Association, the University of Alberta, Glaxo Canada Inc., and Astra Pharmaceuticals.

ALBERTA CITIZENS COME THROUGH

The McCaig Centre for Arthritis and Joint Injury Research *(see page 11)* is another example of community support for AHFMR excellence. Mr. Bud McCaig, President of Trimac and an arthritis sufferer, led a fund-raising campaign to establish the Centre. Over 200 Calgary citizens and corporations donated $2.8 million. AHFMR has given researchers in the group $7.5 million over 10 years, and provided the Heritage Medical Research Building that houses it.

The Calgary community came through in two other projects headed by AHFMR scientists. The Schizophrenia Societies of Canada and citizens of Calgary raised a million dollars for the Ciba-Geigy Chair in Schizophrenia Research. Ciba-Geigy contributed half a million, and the total was matched by the Alberta government. AHFMR has supported the holder of the chair, Dr. Brian MacVicar, for almost 10 years.

Calgary philanthropist, Ms. Jessie Boden Lloyd, has funded the Jessie Boden Lloyd Professorship of Immunology Research, held by Dr. John Reynolds, an AHFMR researcher at the U of C.

AHFMR will continue to coordinate funding for the most efficient use of resources, avoiding duplication of support and capitalizing on complementary funding programs in Alberta, Canada, and around the world.

POWER OF CHOICE:

HOW AHFMR DECIDES WHO TO FUND

AHFMR IS COMMITTED TO SUPPORTING EXCELLENT MEDICAL RESEARCH that will generate knowledge to improve the health and quality of life for Albertans and people throughout the world.

All final decisions about people and projects supported are made by the Trustees, who weigh the mandate to support a balanced program of research that meets standards of excellence against available income, considering that a portion of it must be added to the endowment to conserve purchasing power for the future.

Decisions are made according to AHFMR principles and directed toward the goals. *(See page 89.)*

Network of Advisors

The AHFMR Board of Trustees and executive rely on advice from people in the international, national, and provincial medical research and health communities. Members of the AHFMR Scientific Advisory Council advise on major applications and policy decisions related to research. *(See following page.)* Other scientists and stakeholders in research, education and health serve on AHFMR committees or as consultants.

To be funded, scientists must meet international standards of excellence.

Evaluation by Peers

AHFMR follows the established procedure of evaluating applications by a peer review system. This means applications are judged and rated by other researchers who have esteemed knowledge in the field of the applicant and related areas. Applications are assessed by external reviewers who may be working in any part of the world, and by internal AHFMR committees with representatives from Alberta and other North American universities. The committees then forward their recommendations to the Trustees.

Initially, researchers funded by the Foundation are recruited in cooperation with personnel in the university, hospital or other organization where the researcher will conduct his investigations. Applications are submitted through the host organization and when the researcher is supported by AHFMR, he or she becomes an employee of the host organization, not AHFMR, though AHFMR pays salary and other support.

SCIENTIFIC ADVISORY COUNCIL

Dr. Matthew Spence, President, Alberta Heritage Foundation for Medical Research

Dr. Harold L. Atwood, Professor and Chairman, Department of Physiology, University of Toronto, Toronto, Ontario

Dr. John Bell, Nuffield Professor, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, England

Professor H. John Evans, Director, MRC Clinical and Population Cytogenetics Unit, Western General Hospital, Edinburgh, Scotland

Dr. Wolfgang K. Joklik, Chairman, Department of Microbiology and Immunology, Duke University Medical Centre, Durham, North Carolina (Until June 1991)

Dr. Lloyd D. MacLean, Edward W. Archibald Professor and Chairman, Department of Surgery, McGill University, Montreal, Quebec (Until October 1990)

Dr. Barry C. McBride, Dean, Faculty of Science, University of British Columbia, Vancouver, British Columbia

Dr. Jonathan Meakins, Professor and Chairman, Department of Surgery, McGill University, Montreal, Quebec

Dr. Antony H. Melcher, Vice-Provost, University of Toronto, Toronto, Ontario (Until October 1990)

Dr. I. Barry Pless, Professor of Pediatrics and Epidemiology, McGill University, Montreal, Quebec

Dr. Daniel Porte, Jr., Associate Chief of Staff for Research and Development, Head, Division of Endocrinology and Metabolism, University of Washington, Seattle, Washington

Dr. C. Prives, Professor, Department of Biological Sciences, Columbia University, New York, New York

Dr. Bishnu D. Sanwal, Professor, Department of Biochemistry, The University of Western Ontario, London, Ontario

Dr. René Simard, Vice-President Academic and Research, Université de Montréal, Montreal, Quebec

Dr. Gary L. Stiles, Chief of Cardiology, Duke University Medical Center, Durham, North Carolina

POWER OF PRIORITIES

AHFMR PRINCIPLES

The AHFMR operates according to the following principles:

- Medical research based on international standards of excellence leads to improved health.
- Responsible stewardship of financial resources is necessary to ensure the continuance of the AHFMR for future generations.
- AHFMR holds a public trust and is accountable to the people of Alberta.
- Effective support of medical research requires collaboration among research institutions, granting agencies, governments and the private sector.
- Researchers require a supportive environment to achieve excellence in a highly competitive world of research.
- AHFMR requires autonomy and independence to be effective.

AHFMR GOALS

AHFMR activities are directed toward the following goals:

- To maintain international standards of excellence through an appropriate and effective peer review system.
- To manage expenditures to ensure the continuance of AHFMR for future generations while avoiding significant fluctuations in annual spending.
- To maintain and strengthen basic research in order to discover the underlying causes of disease, and provide a foundation for patient and health research, the practice of medicine and prevention of disease.
- To expand AHFMR support of patient-based and health research in Alberta, and lead new initiatives in these areas.
- To maintain research education and training programs, and encourage young Albertans to pursue research careers.
- To encourage increased collaboration in Alberta, Canada and elsewhere among investigators, research institutions, governments, other granting agencies and the private sector.
- To continue to promote the development of medical research-related economic activities in Alberta, including commercialization of innovation.
- To maintain and improve communication with the public, government, the research community, universities, and health-related institutions.
- To develop a mechanism for the continuing review and updating of the AHFMR strategic plan and for setting priorities.

QUESTIONS TOO IMPORTANT TO LEAVE TO DOCTORS

WHAT ABOUT QUALITY OF LIFE?

TOO OFTEN PHYSICIANS AND PATIENTS HAVE FOCUSED ALMOST EXCLUSIVELY on curing illness and prolonging life at any cost – in dollars or quality of life.

Finally, we are beginning to ask the right question. Does this or that treatment improve the patient's quality of life?

There is even a term for it. QUALYs are quality-adjusted life-years, calculated by finding how much the treatment improved the patient's quality of life then multiplying that by the number of added years.

Dr. John Remmers, AHFMR Scientist and Director of the Centre for the Advancement of Health at the Foothills Hospital in Calgary is a strong advocate for quality of life research. He has integrated it into his own studies of sleep apnea and his patient care. Other Calgary researchers have studied quality of life in hip surgery patients and people with arthritis.

Dr. Remmers defines the issues:

❖ Power to the Patient

"Quality of life is a patient's sense of well-being or perception of minimum impact of disease. We can envision a scale going from complete wellness – and we're never there – to profound illness, so profound that it's worse than death. If you call death zero, we have a scale that can go minus, a fate worse than death. Quality of life is the patient's perception of where he or she lies on that scale.

"We are still in the Dark Ages when it comes to assessing quality of life and there's a great need for it, particularly at this time when we have tremendous constraints placed on our health care budget. Increasingly we need to make hard decisions about which therapies we initiate and which ones really benefit the patient.

"Some decisions are dictated by life and death questions, but often therapeutic questions can be answered only in reference to change and quality of life. At one end of the spectrum, we can talk about life and death and evaluate the quality of life there. At the other end, we have to worry about just how much better the patient feels. Then somewhere in between we have functional improvement we can document.

"We need to evaluate what we do for the patient, what I call 'medical effectiveness': We intervened. Did it help? But let's be more realistic and ask what we really care about. Does the patient feel better?

"We're not used to answering that question. The methodology has only recently come to the fore and it has not moved into hospitals to any great degree....

"In general, physicians feel they need to allow the patient to decide on a therapeutic course, based on advice about what's going to happen to the disease and their quality of life. We are moving away from disease-oriented medicine to patient-oriented medicine.

"We're putting the patients back in the driver's seat again, where they ought to be."

WHAT KIND OF RESEARCH WILL MAKE US HEALTHIER?

Some of us owe our lives to biomedical research, which prevents some diseases and tames others, medicates minds, repairs aging bodies, and generally allows us to live longer. Yet there is no less disease, because health is a matter of sociology as well as biology. Our health depends upon what we eat, what we do, what we think and most of all, how much money we make.

Dr. Matthew Spence, President of AHFMR, talks about what researchers must do to address the intertwined determinants of health:

Our health depends on what we do, what we eat, what we think – and how much money we make.

❖ Jumping the Walls

"I find the present possibilities absolutely breathtaking. Genetics and molecular biology are revolutionizing the face of medicine – we will soon understand the fundamental nature of the genetic programs our parents gave us. At the same time, we are beginning to dimly appreciate the enormous effect of our environment and social fabric on our health and individual well-being.

"The intelligent application of knowledge in both areas could allow us to contemplate a utopia in the future. To realize this utopia, researchers in the biological and medical sciences must jump their walls of traditional disciplines and work with psychologists, sociologists, economists, nutritionists, teachers, nurses, environmentalists, and many others in society.

"The goal of disease prevention through health promotion is critical, but the boundary between public and private responsibility for health remains an issue. Before policy makers can decide whether to endorse regulation of personal behavior in the name of health promotion, they need a better knowledge base.

"We need to be quite certain a particular lifestyle practice can be definitively linked to a health harm. What is the nature of the evidence linking the lifestyle with the harm? What standards of evidence should be required before a causal association is accepted?

"AHFMR supports a range of activity across the continuum, from fundamental laboratory-based research on molecules in biological systems, through patient- and population-based health research, to research on the determinants of human health. The psychological dynamics of status and class, the impact of collective self-esteem and hope on health are grist for the mill. These are not the traditional areas of biomedical research: They are the purview of the humanities and the social sciences.

"Meeting the challenges of improved health takes more than medical researchers. It will take all of us working together, to build a sound knowledge base for society's medical care and for individuals' healthy lifestyle decisions.

THE POWER OF CURIOSITY

"The disease of cancer will be banished from life by calm, unhurrying, persistent men and women, and the motive that will conquer cancer will not be pity nor horror. It will be curiosity to know how and why."

THIS UNIDENTIFIED QUOTATION IS TAPED TO GRANT MCFADDEN'S OFFICE DOOR as a reminder of what drives him in the lab to understand how viruses cause tumors and other diseases. Dr. McFadden leads a 30-member University of Alberta research group investigating the genesis of cancer.

His own research focuses on how poxviruses cause tumors in animals and suppress the immune system. A variety of human cancers have been associated with viruses, and Dr. McFadden has new information that may partially explain how viruses alter the immune system for their own purposes. This may be one way cells become cancerous. Always, new information leads to more questions.

"When you make a career out of research, out of asking questions, you learn that you can never get a complete grip on it. No matter how much you know, it merely expands the horizons in which you are ignorant," says Dr. McFadden.

"That has an appeal for me because I like questions and puzzles, and I like exploring unknown territory. The more you get into research, the more you realize what a fascinating place this is. Nature is quite wonderful and mysterious, and I don't think you can appreciate how wonderful and complex it is until you study it."

"When research is going right, it takes you to places, not only that you've never been before, but places you never knew existed. In our own research, we recently started studying cytokines and other aspects of the human immune system that the rabbit virus we study was never known to interact with. This is a totally new observation. It has led us down the alley of molecular mechanisms viruses use to survive in the world."

Viruses face a hostile world because their hosts have an immune system to destroy viruses. Somehow, viruses learn to circumvent the immune system and reach a state of peaceful co-existence with the host, unless something goes wrong and diseases like AIDS occur.

"The AIDS virus was probably a very benign, quiet monkey virus for millennia. Then for some reason, it hopped species into human beings and now causes a serious disease. To understand how these diseases work, we have to understand the strategies viruses use to survive in the hostile environment. The questions we ask about our virus are very similar to the questions AIDS researchers ask about HIV-1."

Dr. Alexandra Lucas and Dr. Grant McFadden with Matthew, Baron and Seana

Dr. McFadden has found that the rabbit virus has a clever survival strategy. It makes proteins that mimic the receptors of cytokines and tricks the cytokines into thinking they have the correct target. The virus then binds up the cytokines, so that they are inactivated and cannot signal the immune cells to destroy the virus.

"To become a researcher, it is not necessary to be the number one student in class or know how to cure a disease. It's certainly not the stereotype you see in movies – nerds with many colored pencils and lab coats. The essential characteristic is curiosity, being unable to stop until you know something.

"I think that, in the future, more people will be scientists because most of us are born with passionate curiosity. The day-to-day existence can drive that curiosity out of anyone, but if we allow curiosity to grow, it can become a life-long passion and a career – and being a researcher is an exciting life," says Dr. McFadden.

He admits it is also a stressful life, worrying about getting research grants, especially knowing the people in his lab depend upon it. His family is an important balance in his life and their photos are plastered all over his office. "My family keeps my batteries charged," says Dr. McFadden.

The family includes his wife, Dr. Alexandra Lucas, also an AHFMR researcher, daughter Seana, and sons, Baron and Matthew.

Continued . . .

In becoming a physician, Dr. Alexandra Lucas followed a family tradition. Her father, grandfather, and great grandfather were physicians, and her grandmother struck out for new territory as a missionary in China.

"So I was encouraged," says Dr. Lucas, "Maybe I have been brainwashed," she adds, laughing.

Becoming a cardiac physician was not enough because, like her husband, Grant, she wanted to know more.

"It's nice to make people feel better and it's very rewarding – that's why I still do clinical work – but if you do only that, you're basically doing what someone else did 10, 20 years ago. You're not improving things and still too frequently we have to say, 'This is what we think you have, but we really don't know.'"

Dr. Lucas has chosen to learn more about a life and death matter – coronary artery disease. After her specialty training, AHFMR supported her research training at Tufts University New England Medical Centre in Boston to learn more effective ways of diagnosing and treating blocked arteries, which place people at risk for heart attacks and strokes.

"You never know when you will be surprised – that's the fun!"

Currently, arteries are unblocked by various methods, most commonly by cutting away the accumulated plaque in the arteries or squashing back the plaque with a balloon inserted into arteries and inflated. By-pass surgery is used for severe coronary artery disease. Unfortunately, these methods carry some risk, and in a third to half of patients, the arteries become clogged again.

In Boston, Dr. Lucas acquired expertise in a technique called laser-induced fluorescence which can be used to guide laser surgery on the plaque. Dr. Lucas has shown the technique can be used to identify how much fat, fibre and calcium is in the plaque. This could make it possible to tailor therapy to individual needs and monitor the effects of treatment.

"Right now, there is no way to make distinctions. All we can say is 'You've got 30 to 50 percent narrowing of the arteries.We don't know where you will be in five years,'" explains Dr. Lucas.

Has being a woman made it difficult to become a medical researcher?

"There are barriers, but you have to ignore them because if you get wrapped around an axle about that, you concentrate on the problem and not on what you want to do," she says.

"In science, basically someone is paying you to use your imagination, to play and to learn. What's even nicer, you might find something useful and you never know where it's coming from. People don't always discover things by going in a direct line. You never know when you will get surprised and that's the fun."

That's what happened when Dr. Lucas and Dr. McFadden experimented with one of the protein inhibitors from the rabbit virus. When balloon angioplasty is used to push back plaque, the immune system is activated and attempts to seal the arteries back up through an anti-inflammatory response. If the inhibitor protein works for viruses, could it be used to decrease atherosclerosis?

"We tried it in animals just to see what would happen. We had no idea whether it would work: That's where the fascination comes," says Dr. Lucas. It did work and a new avenue of research is opened up with potential to help patients.

"Like her husband, Dr. Lucas has a quotation on her office wall. "*Always do right. It will please some people and astonish the rest.*"

Beside that, she has two other inspirational messages.The first is a poem by Seana which begins "*Dreams. Dreams. Dreams. Dreams are here. Dreams are there. Dreams are everywhere.*" The second is a note from seven year-old Baron: "*I love you Mommy*". At seven months, Matthew can't write yet, but he shows every sign of being mighty curious.

HERITAGE MEDICAL SCIENTISTS

ALLEN, Peter, Ph.D., Department of Applied Sciences in Medicine, Faculty of Medicine, University of Alberta. *"The in vivo application of NMR to medicine"*

ANDREWS, Brian, Ph.D., Department of Applied Sciences in Medicine, Faculty of Medicine, University of Alberta. *"Applied neural control"*

BLEACKLEY, Robert, Ph.D., Department of Biochemistry, Faculty of Medicine, University of Alberta. *"A molecular analysis of cell-mediated cytotoxicity, bench to bedside"*

BRINDLEY, David, Ph.D., Department of Biochemistry, Faculty of Medicine, University of Alberta. *"Control of glycerolipid and lipoprotein metabolism"*

BULLOCH, Andrew, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Modulation of neurite outgrowth by adult neurons"*

DUFF, Henry, M.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Mechanistic approach to antiarrhythmic therapy"*

FIELD, L. Leigh, Ph.D., Department of Pediatrics, Faculty of Medicine, University of Calgary. *"Genetic analysis of several common multifactorial diseases"*

FRITZLER, Marvin, M.D., Ph.D., Departments of Medicine and Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Autoantibodies in rheumatic diseases"*

GILES, Wayne, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Electrophysiology-pharmacology of cardiac cells"*

GORDON, Tessa, Ph.D., Department of Pharmacology, Faculty of Medicine, University of Calgary. *"Neuromuscular plasticity and function after nerve injuries"*

GRIFFITHS, Derek, Ph.D., Department of Applied Sciences in Medicine, Faculty of Medicine, University of Alberta. *"Urodynamics"*

HULLIGER, Manuel, Ph.D., Departments of Clinical Neurosciences and Medical Physiology, Faculty of Medicine, University of Calgary. *"Peripheral control of voluntary movement"*

IATROU, Kostas, Ph.D., Department of Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Chorion of* Bombyx mori *as model system for study of organization, expression and evolution of eukaryotic multigene family"*

JIMBOW, Kowichi, M.D., Ph.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Melanogenesis, and laboratory diagnosis and rational therapy of malignant melanoma"*

JUGDUTT, Bodh, M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Modification of ventricular geometry and function after myocardial infarction: effect of nitroglycerin and age-inhibitor"*

MARTIN, Renee, Ph.D., Department of Pediatrics, Faculty of Medicine, University of Calgary. *"Cytogenetic and molecular analysis of human sperm"*

McFADDEN, Grant, Ph.D., Department of Biochemistry, Faculty of Medicine, University of Alberta. *"Studies on the replication and biology of leporipoxviruses"*

McGHEE, James, Ph.D., Department of Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Outline of the plan of the growth and development research group in the area of gene expression"*

PATERSON, Malcolm, Ph.D., Department of Medicine, Cross Cancer Institute. *"Clinical genetics and molecular carcinogenesis"*

PAUL, Leendert, M.D., Ph.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Organ transplant: program of clinical and experimental research"*

PITTMAN, Quentin, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Hypothalamic control of autonomic and endocrine function"*

PROCHAZKA, Arthur, Ph.D., Department of Physiology, Faculty of Medicine, University of Alberta. *"Neural control of movement"*

RABINOVITCH, Alexander, M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Immunobiology of diabetes mellitus"*

REMMERS, John, M.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Control of breathing in health and disease"*

***SCHNEIDER**, Wolfgang, Ph.D., Department of Biochemistry, Faculty of Medicine, University of Alberta. *"Receptor-mediated endocytosis in oocytes"*

SINGH, Bhagirath, Ph.D., Department of Immunology, Faculty of Medicine, University of Alberta. *"Molecular and functional analysis of T Cell antigen interactions"*

TAYLOR, Diane, Ph.D., Department of Medical Microbiology and Infectious Diseases, Faculty of Medicine, University of Alberta. *"Genetic studies of bacterial plasmids,* campylobacter *and* helicobacter*"*

TER KEURS, Henk, M.D., Ph.D., Departments of Medicine and Medical Physiology, Faculty of Medicine, University of Calgary. *"Control of cardiac function in normal and in diseased myocardium"*

TYBERG, John, M.D., Ph.D., Departments of Medicine and Medical Physiology, Faculty of Medicine, University of Calgary. *"Left ventricular external constraint, venous capacitance and other stories"*

VANCE, Dennis, Ph.D., Department of Biochemistry, Faculty of Medicine, University of Alberta. *"Phospholipid and lipoprotein metabolism"*

WALSH, Michael, Ph.D., Department of Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Mechanisms of regulation of smooth muscle contraction"*

WANG, Jerry, Ph.D., Department of Medical Biochemistry, Faculty of Medicine, University of Calgary. *"The studies of signal transduction"*

YOON, Ji-Won, Ph.D., Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary. *"Role of viruses and autoimmunity in the pathogenesis of insulin-dependent diabetes mellitus"*

YOUNG, James, Ph.D., Department of Physiology, Faculty of Medicine, University of Alberta. *"Molecular mechanisms of membrane transport"*

* Cancelled during 1990/92

HERITAGE MEDICAL SCHOLARS

*ACHESON, Ann, Ph.D., Department of Anatomy and Cell Biology, Faculty of Medicine, University of Alberta. *"Role of cell adhesion in neurotransmitter phenotypic expression"*

ANDERSON, M. John, Ph.D., Department of Anatomy, Faculty of Medicine, University of Calgary. *"Transduction of inductive signals during synaptogenesis"*

ANDERSON, Robert, Ph.D., Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary. *"Membrane structure, function and response to cell-killing activities"*

AUER, Roland, M.D., Ph.D., Department of Pathology, Faculty of Medicine, University of Calgary. *"Excitotoxicity in ischemia and related conditions"*

BARNES, Steven, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Mechanisms of synaptic interaction among photoreceptors of the vertebrate retina"*

BAZETT-JONES, David, Ph.D., Departments of Anatomy and Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Structure of the transcription complex"*

BEFUS, Dean, Ph.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Mast cell biology: neuroimmunology and mucosal immunity in parasitic infections"*

BENISHIN, Christina, Ph.D., Department of Physiology, Faculty of Medicine, University of Alberta. *"Endogenous and exogenous regulators of ion channels"*

BERDAN, Robert, Ph.D., Department of Physiology, Faculty of Medicine, University of Alberta. *"Formation and function of electrical synapses"*

*BOISVERT, Donald, M.D., Ph.D., Department of Surgery, Faculty of Medicine, University of Alberta. *"Functional and biochemical aspects of brain edema"*

BOWLING, Douglas, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Geniculo-cortical organization in LGN"*

CAMPENOT, Robert, Ph.D., Department of Anatomy and Cell Biology, Faculty of Medicine, University of Alberta. *"Control of nerve growth and growth-related gene expression in peripheral neurons in compartmented cultures"*

CLANDININ, Michael, Ph.D., Departments of Foods and Nutrition and Medicine, Faculties of Home Economics and Medicine, University of Alberta. *"Nutrition and metabolism of diet fat"*

CODDING, Penelope, Ph.D., Departments of Chemistry and Pharmacology and Therapeutics, Faculties of Science and Medicine, University of Calgary. *"Structural and molecular modeling studies by drug-receptor interactions and proteins"*

COLMERS, William, Ph.D., Department of Pharmacology, Faculty of Medicine, University of Alberta. *"Neuromodulation in CNS"*

*DAY III, Rufus, Ph.D., Department of Medicine, Cross Cancer Institute. *"DNA repair and gene regulation in human tumor systems"*

DEREWENDA, Zygmunt, Ph.D., Department of Biochemistry, Faculty of Medicine, University of Alberta. *"Structure-function relationships in lipolytic enzymes"*

DUNN, Susan, Ph.D., Department of Pharmacology, Faculty of Medicine, University of Alberta. *"Mechanisms of GABAergic neurotransmission"*

EASTON, Paul, M.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Hypoxia, respiratory muscles and ventilatory control"*

EDWARDS, Dylan, Ph.D., Departments of Pharmacology and Therapeutics and Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Growth factor control of gene regulation"*

EGGERMONT, Jos, Ph.D., Department of Psychology, Faculty of Social Sciences, University of Calgary. *"Maturation of neural interaction in the cortex"*

ELLIOTT, John, M.D., Ph.D., Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Alberta. *"Cloning of genes for malaria surface antigens by eukaryotic expression"*

FAMIGLIETTI, Edward, M.D., Ph.D., Department of Anatomy, Faculty of Medicine, University of Calgary. *"Development, regeneration and functional organization of vertebrate retina"*

FEWELL, James, Ph.D., Departments of Obstetrics and Gynecology and Medical Physiology, Faculty of Medicine, University of Calgary. *"Arousal response to cardiorespiratory stimuli"*

FINEGOOD, Diane, Ph.D., Departments of Medicine and Physiology, Faculty of Medicine, University of Alberta. *"Regulation and interactions of the factors determining metabolic control"*

FLIEGEL, Larry, Ph.D., Department of Pediatrics, Faculty of Medicine, University of Alberta. *"Ion exchangers of heart sarcolemma"*

FRANK, Cyril, M.D., Ph.D., Department of Surgery, Faculty of Medicine, University of Calgary. *"Connective tissue (ligament) structure, function and homeostasis"*

FRENCH, Robert, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Ion channels of excitable membranes"*

FUJITA, Donald, Ph.D., Department of Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Structure, regulation and function of the human c-src gene, its product pp60c-src and other tyrosine kinases"*

*GALLIN, Warren, Ph.D., Department of Zoology, Faculty of Science, University of Alberta. *"Cellular mechanisms of development"*

GARBER, Anthony, Ph.D., Departments of Pediatrics & Medical Biochemistry, Faculty of Medicine, University of Calgary. *"The molecular biology of psoriasis"*

*GELLMAN, Reuben, Ph.D., Departments of Clinical Neurosciences and Medical Physiology, Faculty of Medicine, University of Calgary. *"Processing of oculomotor signals in the cerebellum"*

GODBOUT, Roseline, Ph.D., Department of Molecular Genetics, Cross Cancer Institute. *"Molecular genetics of retinal development"*

*GREEN, Douglas, Ph.D., Department of Immunology, Faculty of Medicine, University of Alberta. *"Immunoregulatory T cells and molecules"*

GREENSHAW, Andrew, Ph.D., Department of Psychiatry, Faculty of Medicine, University of Alberta. *"Biogenic amine receptors in psychiatric disorders"*

GREER, John, Ph.D., Department of Physiology, Faculty of Medicine, University of Alberta. *"Development of neuronal mechanisms controlling breathing"*

* Cancelled during 1990/92

HART, David, Ph.D., Departments of Medicine and Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary. *"Role of plasminogen activators and their inhibitors in normal and disease processes"*

HAYNES, Lawrence, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Properties of the cGMP-gated channel of vertebrate rods and cones"*

***HOFFER**, J. Andy, Ph.D., Departments of Medical Physiology and Clinical Neurosciences, Faculty of Medicine, University of Calgary. *"Neural control of movements"*

***HULBERT**, William, Ph.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Mechanisms of acute airway injury and repair: physiology,morphology, cell biology"*

JACOBS (KAUFMAN), Susan, Ph.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Control mechanisms of fluid and electrolyte balance"*

***JENSEN**, Susan, Ph.D., Department of Medical Microbiology and Infectious Diseases, Faculty of Science, University of Alberta. *"Biosynthesis of novel penicillin and cephalosporin antibiotics"*

KANE, Kevin, Ph.D., Department of Immunology, Faculty of Medicine, University of Alberta. *"Molecular interactions governing cytotoxic T cell recognition and transmembrane signalling"*

KARGACIN, Gary, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Structural properties of contracting smooth muscle"*

KING, Malcolm, Ph.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Studies on mucus secretion and clearance"*

KOOPMANS, Henry, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Internal control of energy balance"*

KUBES, Paul, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Polymorphonuclear leukocyte-endothelial cell interactions: the role of nitric oxide"*

LAFRENIERE, Rene, M.D., Department of Surgery, Faculty of Medicine, University of Calgary. *"Murine liver large granular lymphocytes and their role against experimental hepatic neoplasms"*

LEE, Patrick, Ph.D., Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary. *"The mechanism of virus attachment to host cells"*

***LEE**, Timothy, Ph.D., Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary. *"Protective immunity of nematode infection"*

LESKIW, Brenda, Ph.D., Department of Microbiology, Faculty of Science, University of Alberta. *"The BldA gene and its role in antibiotic production and morphological differentiation"*

LOPASCHUK, Gary, Ph.D., Department of Pediatrics and Pharmacology, Faculty of Medicine, University of Alberta. *"Fatty acid metabolism in the heart"*

MacVICAR, Brian, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Synaptic and non-synaptic mechanisms controlling neuronal excitability"*

MAINS, Paul, Ph.D., Department of Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Molecular and genetic analysis of C. elegans embryogenesis"*

MANTLE, Michele, Ph.D., Departments of Medical Biochemistry and Pediatrics, Faculty of Medicine, University of Calgary. *"Intestinal mucin: structure, synthesis and secretion"*

MARTIN-IVERSON, Mathew, Ph.D., Department of Psychiatry, Faculty of Medicine, University of Alberta. *"Behavioral functions of dopamine receptor subtypes: animal models of schizophrenia, Parkinson's disease"*

MICHALAK, Marek, Ph.D., Departments of Pediatrics and Biochemistry, Faculty of Medicine, University of Alberta. *"Structure and function of membrane proteins"*

MILLER, Freda, Ph.D., Department of Anatomy and Cell Biology, Faculty of Medicine, University of Alberta. *"Molecular analysis of neuronal development"*

MITCHELL, L. Brent, M.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Human ventricular tachyarrhythmias: a mechanistic evaluation of therapeutics"*

MOORE, Graham, Ph.D., Department of Pharmacology and Therapeutics, Faculty of Medicine, University of Calgary. *"Bioactive confirmation, receptor recognition, and design of mimetics"*

NEWMAN, Stephen, M.D., Department of Psychiatry, Faculty of Medicine, University of Alberta. *"Mortality of affective disorder patients in Alberta"*

OLSON, David, Ph.D., Department of Obstetrics and Gynecology, Faculty of Medicine, University of Alberta. *"Eicosanoid synthesis and function in perinatal physiology"*

OSTERGAARD, Hanne, Ph.D., Department of Immunology, Faculty of Medicine, University of Alberta. *"CD45 protein tyrosine phosphatase: role in T cell activation"*

PARHAD, Irma, M.D., Departments of Pathology and Clinical Neurosciences, Faculty of Medicine, University of Calgary. *"Neurofilament gene expression and regulation in models of neurofibrillary degeneration"*

PASDAR, Manijeh, Ph.D., Department of Anatomy and Cell Biology, Faculty of Medicine, University of Alberta. *"Regulation of desmosome assembly in MDCK epithelial cells"*

PREIKSAITIS, Jutta, M.D., Departments of Medicine and Medical Microbiology and Infectious Diseases, Faculty of Medicine, University of Alberta. *"Cytomegalovirus and Epstein Barr virus infection in allograft and transfusion recipients: epidemiology and pathogenesis"*

RASMUSSEN, Colin, Ph.D., Department of Anatomy and Cell Biology, Faculty of Medicine, University of Alberta. *"Molecular genetic analysis of calmodulin-dependent cell cycle control"*

RATTNER, Jerome, Ph.D., Departments of Medical Biochemistry and Anatomy, Faculty of Medicine, University of Calgary. *"Centromere structure"*

READ, Randy, Ph.D., Department of Medical Microbiology and Infectious Diseases, Faculty of Medicine, University of Alberta. *"Protein crystallography and rational design of trypanocidal drugs"*

REHA-KRANTZ, Linda, Ph.D., Department of Genetics, Faculty of Science, University of Alberta. *"DNA polymerase structure-function studies"*

REYNOLDS, John, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Contribution of Peyer's patches to the immune system"*

RIABOWOL, Karl, Ph.D., Department of Medical Biochemistry, Faculty of Medicine, University of Calgary. *"The FOS protein complex in transcription and transformation"*

RICE, Stephen, Ph.D., Department of Biochemistry, Faculty of Medicine, University of Alberta. *"Molecular biology of a herpes simplex virus regulatory protein"*

RORSTAD, Otto, M.D., Ph.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Studies on vasocative intestinal peptide(VIP)"*

ROSENBERG, Susan, Ph.D., Department of Molecular Genetics and Carcinogenesis Laboratory, Cross Cancer Institute. *"Homologous recombination and mutation in human cells and in escherichia coli"*

RYAN, Robert, Ph.D., Department of Biochemistry, Faculty of Medicine, University of Alberta. *"Hormone-induced diacylglycerol transport and metabolism"*

SCHNETKAMP, Paul, Ph.D., Department of Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Molecular components of signal transduction in retinal rods"*

SCHRYVERS, Anthony, M.D., Ph.D., Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary. *"The receptors for human transferrin and lactoferrin in Neisseria meningitidis"*

SCHÜRCH, Samuel, Ph.D., Departments of Medicine and Medical Physiology, Faculty of Medicine, University of Calgary. *"Pulmonary surfactant: lung stability and particle clearance, cell adhesion"*

SCOTT, R. Brent, M.D., Department of Pediatrics, Faculty of Medicine, University of Calgary. *"Intestinal motility"*

SEVERSON, David, Ph.D., Department of Pharmacology and Therapeutics, Faculty of Medicine, University of Calgary. *"Metabolic regulation and signal transduction"*

SHARKEY, Keith, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"GI afferent nerves and inflammation"*

SIMINOSKI, Kerry, M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Regulation of nerve growth factor activity"*

SMITH, Peter, Ph.D., Department of Pharmacology, Faculty of Medicine, University of Alberta. *"Mechanism of action of neuromodulators and trophic factors"*

SNYDER, Floyd, Ph.D., Departments of Medical Biochemistry and Pediatrics, Faculty of Medicine, University of Calgary. *"Inherited disorders of nucleotide metabolism"*

SOKOL, Pamela, Ph.D., Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary. *"Structure, function and regulation of Pseudomonas Aeruginosa ferripyochelin binding protein"*

SPENCER, Charlotte, Ph.D., Department of Biochemistry, Faculty of Medicine, University of Alberta. *"Transcription initiation and elongation in the human C-MY-C-Oncogene"*

STEVENSON, Bruce, Ph.D., Department of Anatomy and Cell Biology, Faculty of Medicine, University of Alberta. *"Molecular dynamics of ZO-1 and the tight junction"*

STONE, James, Ph.D., Department of Biochemistry, Faculty of Medicine, University of Alberta. *"Genetics of RAS"*

SYED, Naweed, Ph.D., Department of Anatomy, Faculty of Medicine, University of Calgary. *"Mechanisms underlying synaptogenesis"*

***TETZLAFF**, Wolfgang, M.D., Ph.D., Department of Anatomy, Faculty of Medicine, University of Calgary. *"Gene expression in lesioned neurons of the CNS and PNS"*

TURNER, Raymond, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Conditional bursting circuit in avertebrate sensory system"*

VOGEL, Hans, Ph.D., Department of Biochemistry and Biological Sciences, Faculty of Science, University of Calgary. *"NMR and the regulation of metabolism"*

WAISMAN, David, Ph.D., Department of Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Covalent regulation of Ca2-binding proteins"*

WALLACE, John, Ph.D., Department of Medical Physiology, Faculty of Medicine, University of Calgary. *"Endogenous mediators of gastrointestinal pathophysiology"*

WARNOCK, Garth, M.D., Department of Surgery, Faculty of Medicine, University of Alberta. *"Studies of the isolation and transplantation of islets for type I diabetes"*

WENMAN, Wanda, M.D., Department of Pediatrics, Faculty of Medicine, University of Alberta. *"Pathogenesis of human chlamydia infections"*

WINDHORST, Uwe, M.D., Department of Clinical Neurosciences and Medical Physiology, Faculty of Medicine, University of Calgary. *"Integration of recurrent inhibition and propriospinal feedback"*

WITKOWSKI, Francis, M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Clinical and basic applications of cardiac electrical mapping"*

WONG, Norman, M.D., Department of Medicine, Faculty of Medicine, University of Calgary. "Nuclear mechanism of thyroid hormone action"

WONG, Sui-Lam, Ph.D., Department of Biological Sciences, Faculty of Science, University of Calgary. *"Engineering of a bacterial expression and secretion system and its application for the production of proteins"*

***WOODS**, Donald, Ph.D., Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary. *"Pathogenesis of pseudomonas aeruginosa disease"*

WYSE, George, M.D., Ph.D., Departments of Medicine and Pharmacology and Therapeutics, Faculty of Medicine, University of Calgary. *"Patient-based studies of pathophysiology of human essential hypertension and the management of cardiac dysrhythmias"*

YAO, Zemin, Ph.D., Department of Biochemistry, Faculty of Medicine, University of Alberta. *"Apolipoprotein B expression: structure and function studies"*

YOKOYAMA, Shinji, M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Mechanism of reverse cholesterol transport"*

YOUNG, Dallan, Ph.D., Department of Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Investigation of signal transduction pathways in the fission yeast schizosaccharomyces pombe and mammals"*

ZACKSON, Saul, Ph.D., Department of Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Cellular and molecular analysis of a morphogenetic cell migration"*

ZERNICKE, Ronald, Ph.D., Department of Surgery, Faculty of Medicine, University of Calgary. *"Functional adaptation of bone"*

ZWIERS, Hindrik, Ph.D., Departments of Medical Physiology and Medical Biochemistry, Faculty of Medicine, University of Calgary. *"Neuropeptides, phosphoproteins, and neural plasticity"*

HERITAGE CLINICAL INVESTIGATORS

BELL, Robert, M.D., Department of Clinical Neurosciences, Faculty of Medicine, University of Calgary. *"Mapping of non-major histocompatibility complex genetic susceptibility in multiple sclerosis"*

***BERTHIAUME**, Yves, M.D., Department of Medicine, Faculty of Medicine, University of Calgary. *Mechanisms of alveolar liquid clearance"*

BRAY, Robert, M.D., Department of Surgery, Faculty of Medicine, University of Calgary. *"Revascularization and ligament healing"*

BROWN, Christopher, M.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Structure/function relationships of granulocyte-macrophage colony-stimulating factor and its receptor"*

BUTZNER, J. Decker, M.D., Department of Pediatrics, Faculty of Medicine, University of Calgary. *"Adaptation of the intestinal epithelium: response to malnutrition and inflammation"*

CHIK, Constance, M.D., Ph.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Ethanol action on neurotransduction mechanisms"*

COCKFIELD, Sandra, M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"The regulation of interferon-T and other cytokines in vivo"*

COE, James, M.D., Department of Pediatrics, Faculty of Medicine, University of Alberta. *"Pharmacological manipulation of the neonatal circulation"*

***FEDORAK**, Richard, M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Adaptation and regulation of intestinal glucose transport"*

FLETCHER, William, M.D., Department of Clinical Neurosciences, Faculty of Medicine, University of Calgary. *"The diagnosis of vestibular disorders"*

GILLIS, Anne, M.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Ventricular dysfunction and antiarrhythmic drug pharmacodynamics"*

GRUNDY, Paul E., M.D., Department of Molecular Genetics and Carcinogenesis Laboratory, Cross Cancer Institute. *"Molecular genetic analysis of Wilms' Tumor"*

HO, May, M.D., Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary. *"Immunoregulation in Falciparum malaria"*

KAVANAGH, Katherine, M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Mechanisms of cardiac defibrillation and cardioversion"*

KIMBERLEY, Barry, M.D., Ph.D., Department of Surgery, Faculty of Medicine, University of Calgary. *"Mechanisms of auditory dysfunction"*

KNETEMAN, Norman, M.D., Department of Surgery, Faculty of Medicine, University of Alberta. *"Islet isolation, immunodulation and immunosuppression"*

KUNIMOTO, Dennis, M.D., Department of Medical Microbiology and Infectious Diseases, Faculty of Medicine, University of Alberta. *"IgA regulation"*

LEE, B. Craig, M.D., Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary. *"The role of hemoglobin iron acquisition in the pathogenesis of gonococcal infection"*

LEE, Samuel, M.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Pathophysiology of portal hypertension"*

LIEN, Dale, M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Neutrophils in airway inflammation"*

LUCAS, Alexandra R., M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Laser-induced fluorescence: a diagnostic tool for cardiovascular disease"*

MAKSYMOWYCH, Wolodymyr, M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"T-cell antigen receptor genes in rheumatoid arthritis"*

MEDDINGS, Jonathan, M.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Physiology of intestinal permeability"*

MODY, Christopher, H., M.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Antimicrobial defense mechanisms of the lung in CD 4 (T-helper/inducer) cell deficiency"*

***PARFREY**, Nollaig, M.D., Department of Pathology, Faculty of Medicine, University of Alberta. *"Immune mechanisms in self tolerance and autoimmunity"*

PENN, Andrew, M.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Mitochondrial failure and neuronal dropout in Parkinson's disease"*

TEO, Koon, Ph.D., Department of Medicine, Faculty of Medicine, University of Alberta. *"Clinical trials in cardiovascular diseases"*

TRANMER, Bruce, M.D., Department of Clinical Neurosciences, Faculty of Medicine, University of Calgary. *"The role of hypervolemic hemodilution during cerebral ischemia"*

TREDGET, Edward, M.D., Department of Surgery, Faculty of Medicine, University of Alberta. *"Collagen metabolism in vivo"*

VAN AERDE, Johny, M.D., Department of Pediatrics, Faculty of Medicine, University of Alberta. *"Fat utilization in parenterally fed newborn infants, measured with indirect calorimetry and with tracer kinetics of 13"*

WATSON, Timothy W., M.D., Ph.D., Department of Clinical Neurosciences, Faculty of Medicine, University of Calgary. *"Somatostatin actions in the in vitro striatal slice"*

WOODMAN, Richard, M.D., Department of Medicine, Faculty of Medicine, University of Calgary. *"Identification and functional characterization of neutrophil antibodies and their associated antigens"*

ZOCHODNE, Douglas, M.D., Department of Clinical Neurosciences, Faculty of Medicine, University of Calgary. *"Diabetic nerve and ganglion microenvironment"*

* Cancelled during 1990/92

POWER OF APPROVAL

"Since the Foundation has been in existence, it has undoubtedly changed the medical research landscape in Alberta. It has a proud record of accomplishment in attracting to the province a cadre of scientific talent that rivals the best, anywhere in the world."

Dr. Henry Friesen
President, Medical Research Council of Canada

"The AHFMR has played a crucial role in the development of biomedical science and has placed Alberta's university-based research amongst the very best in the country. Lionel McLeod would have been very proud of how much has been accomplished in such a short period of time."

Dr. Albert Aguayo
Centre for Research in Neuroscience, McGill University

"The University of Alberta Hospitals prides itself on being at the leading edge of new developments in medical care. Much of the credit must go to the AHFMR which has supported the recruitment of world leaders and provided them with continuing research support."

Mr. Don Schurman,
President, University of Alberta Hospitals

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"THE POWER AND THE PROMISE"

Student Study Guide

(See Reverse side for questions)

STUDY QUESTIONS

I. Would I like to be a Medical Researcher?

Read the personal stories on pages 6, 27, 34, 73, 75, & 92). Discuss:

1. Is there a "science personality"?
2. Do you have to be brilliant or a nerd to be a scientist?
3. What seems to attract people to medical research careers?

II. The Brain

1. What are the "chemicals of the mind?" (Page 23)
2. Can nerve cells injured or destroyed by Alzheimer's, or some other disease, ever come back to life? (Page 29, 30)
3. How can scientists watch the brain think? (Page 27, 28)
4. Why does electricity help the paralyzed move? (Pages 29-32)

III. Genes

1. Are Mendel's laws of heredity always true? (Page 56)
2. What is genetic engineering? How is it helpful in medicine?
3. If you have a gene for a disease, does that necessarily mean you will get it? (Page 55)
4. Once genes for a disease are discovered, name three ways that could be applied to preventing, curing, or managing the disease? (Pages 61-64)
5. Would you let someone do gene therapy on you? (Pages 55-64)
6. How could information about your genes be misused? (Page 58)

IV. The Immune System

1. Your immune system is healing you this very minute, but sometimes it destroys the body. Name three situations where it works against us. (Pages 40, 42, 46)
2. How does a killer immune cell kill a tumor cell? (Pages 40-42, 44)
3. Are food allergies real or imagined? (Page 46)
4. Could there be a vaccine for cancer or diabetes? (Pages 48, 49, 52)

V. Cancer

1. What causes cancer? (65, 66)
2. How does a tumor suppressor gene keep you from getting cancer? (Page 66)
3. Name two new cancer treatments based on the immune system. (Page 67)

VI. Heart

1. If your blood vessels were unravelled, how far would they reach? (Page 15)
2. What makes your heart beat? (Page 15)
3. Even if you ate the perfect diet, you might still have high cholesterol. Why? (Page 19)

AHFMR
TRIENNIAL REPORT
FINANCIAL STATISTICS

Alberta Heritage
Foundation for
Medical Research

3125 ManuLife Place
10180 - 101 Street
Edmonton, Alberta T5J 3S4

HOW IS AHFMR FINANCED?

The Foundation operates on a portion of the interest revenue from an endowment fund, which is managed by Alberta Treasury. This endowment was established by the Government of Alberta in 1980 with an initial investment of $300 million. The remaining portion of the interest revenue earned each year is retained within the endowment to help maintain the value of the fund in terms of spending power. Market value varies but as at March 1993, the market value of the endowment fund was $626 million. In terms of 1980 dollars, this is worth about $313 million.

HOW DOES THE FOUNDATION DECIDE HOW MUCH TO SPEND?

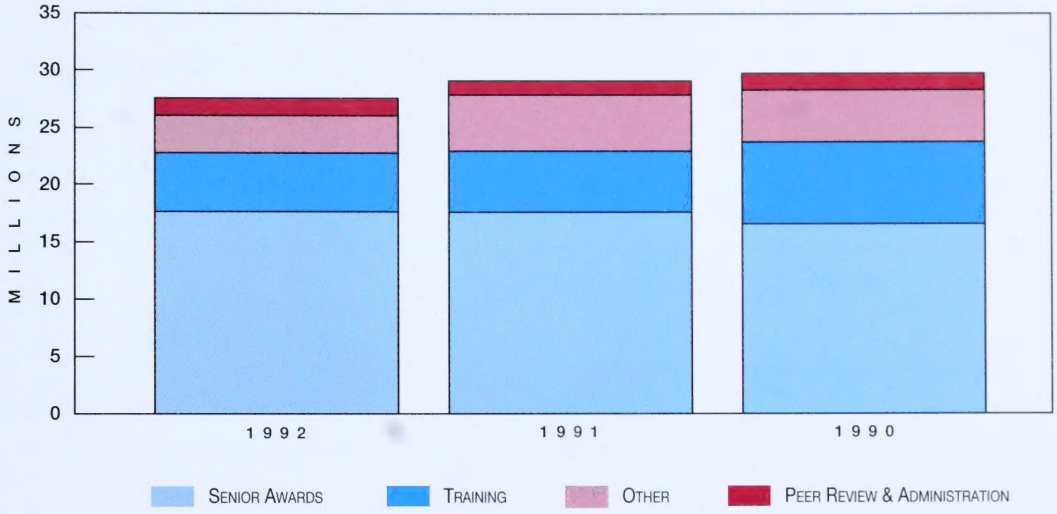
Final decisions about Foundation spending are made by the Trustees who weigh the mandate to support a balanced program of research that meets standards of excellence against available income, considering that a portion of the income must be added to the endowment to conserve purchasing power for the future.

HOW DOES THE FOUNDATION MANAGE FUNDS RECEIVED FROM THE ENDOWMENT?

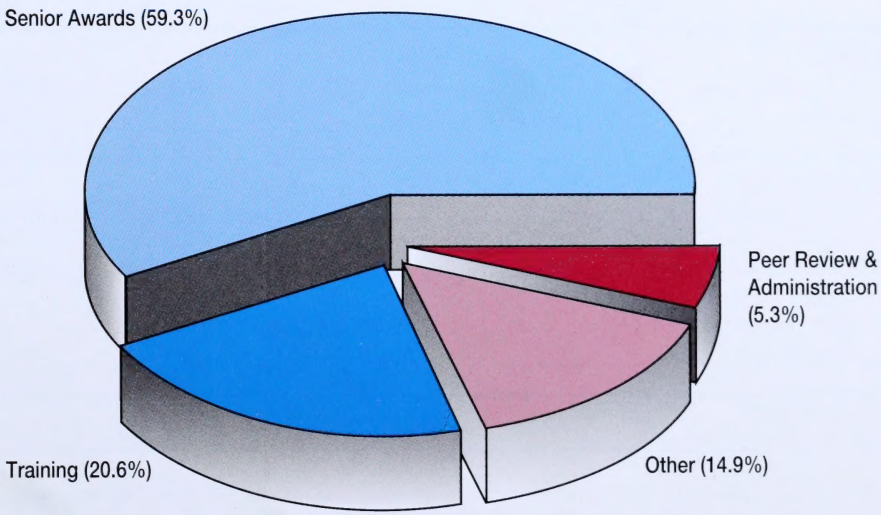
Management maintains a system of internal accounting controls, external financial relationships, financial planning and forecasting models. Financial statements are prepared by management following generally accepted accounting principles and are independently audited by the Auditor General of Alberta. The information contained in the financial statements is the responsibility of management. The Finance Committee of the Board of Trustees meets with management regularly to review financial results, annual budgets, and projections, and with the auditors annually to review the findings of the audit and approve the financial statements. The Finance Committee reports to the full Board of Trustees on a regular basis.

EXPENDITURE SUMMARY

$ BY YEAR 1990-92



PERCENTAGE FOR THE THREE YEARS



Continued on back page

SUMMARY OF BALANCE SHEETS

for the 3 years as at March 31

(SEE ANNUAL REPORTS FOR DETAILS)

	1992	1991	1990
ASSETS			
Cash	$7,298,002	$ 9,149,155	$7,764,986
Accounts receivable	40,110	107,895	86,521
Advances and prepaid expenses	425,513	371,423	537,494
Mortgages receivable	291,959	459,374	376,243
Capital assets	258,367	135,686	112,245
Deferred pension costs	74,317	87,616	
	$8,388,268	$10,311,149	$8,877,489
LIABILITIES, SURPLUS AND UNEXPENDED FUNDS			
Accounts Payable	$880,768	1,591,250	4,566,898
Revenue Surplus	2,697,796	3,647,497	926,637
Medical Innovation Program unexpended funds (1)	4,809,704	5,072,402	3,383,954
	$8,388,268	$10,311,149	$8,877,489

(1) The Foundation administers funds for this program on behalf of the Government of Alberta. Total receipts to the program for the three years were $7,423,808 and expenditures for the three years were $2,614,104.

SUMMARY OF REVENUE AND EXPENDITURE

for the 3 years ending March 31

(SEE ANNUAL REPORTS FOR DETAILS)

	1992	1991	1990	3 Year Total
REVENUE				
Endowment transfers	$26,000,000	$31,000,000	$34,000,000	$91,000,000
Interest	532,973	653,187	777,015	1,963,175
	$26,532,973	$31,653,187	$34,777,015	$92,963,175
EXPENDITURES				
Senior Research Awards Scientists, Scholars, Clinical Investigators	17,264,198	17,277,865	16,585,028	51,127,091
Research Training Awards Students & Fellows	5,154,858	5,338,123	7,269,825	17,762,806
Other Programs (1)	3,358,447	4,906,293	4,550,803	12,815,543
Administration	1,705,171	1,410,046	1,454,382	4,569,599
	$27,482,674	$28,932,327	$29,860,038	$86,275,039
(Deficiency) excess of revenue over expenditures (2)	$ (949,701)	$ 2,720,860	$ 4,916,977	$ 6,688,136

(1) These include Health care research Major equipment, Independent establishment, Institutional grants, Conference support, Special initiatives, Visiting scientists & professors, Technical workshops, Computer and Library support, and Technology commercialization.

(2) In addition to the expenditures listed for 1990, a final payment of $3,668,372 was made regarding the Heritage research buildings at U of C and U of A constructed in 1987.

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FOUNDATION FOR
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